REMARKS

Claims 1-66 are pending. Claims 1-7, 10, 15-22, 31-42, 45, 50-55 and 64-66 are withdrawn from consideration as being drawn to non-elected inventions. Claims 8, 9, 23, 24, 25, 26, 28, 43, 44, 47, 56, 57, 58, 59, and 61 have been amended to better clarify aspects of the invention. Claims 11, 12, 13, 14, 27, 29, 30, 46, 48, 49, 60, 62 and 63 have been canceled without prejudice or disclaimer. New claims 67-70 have been added for consideration. Support for the new claims can be found throughout the specification and in the original claims as filed. Support for the amendments can be found throughout the specification, but in particular, on page 26, paragraphs [0070] and [0071]. No new matter has been entered by way of this amendment. Accordingly, if the new claims are entered for consideration, claims 1-10, 12, 15-26, 28, 31-45, 47, 50-59, 61, 64-70 are pending. Reconsideration of this application is respectfully requested.

Requirement for Restriction/Election

Due to the complexity of the supplemental requirement for restriction, for which Applicant provided a response on June 17, 2005, the Examiner has provided a summary of the supplemental requirement for restriction and has requested confirmation of Applicant's election of groups and the combination of agents on which Applicant wishes to pursue examination. Pursuant to the Examiner's request, Applicant confirms that Applicant wishes to elect the invention of:

Section A (the at least one first agent): Group I, claims 1, 23, 36 and 56, wherein the at least one first agent is minocycline or any tetracycline family derivative capable of crossing the blood brain barrier,

Section B (the at least one second agent, which is an anti-inflammatory): Group XVIII, claims 23, 36 and 56, wherein the at least one second agent is salicylates.

Section C (the at least one second agent, (now noted as the third agent) which is an inhibitor of glutamate induced excitotoxicity): Group XXII, claims 28 and 61, wherein the at least one second agent is memantine.

With respect to the requirement for choosing one of the four possible combinations of agents, Applicant elects the combination noted in 4) one agent of Section

A in combination with one agent of Section B in combination with one agent of Section C.

In addition, Applicant requests rejoinder of claims 15, 16, 17, 18, 31, 32, 33, 34, 50, 51, 64 and 65, with the claims currently under prosecution, since they read on the subject matter (anti-inflammatory agents) of the claims currently elected for prosecution. Applicant believes that they were inadvertently left out of the list of claims noted by the Examiner. Accordingly, rejoinder of these claims is believed to be in order and is courteously requested.

Objection to the Specification

The Examiner has objected to the specification because of the following informalities:

The word "functional" is misspelled in the title of Table 1 at the top of page 8 of the disclosure. The word "tetracycline" is misspelled on page 19, paragraph [0048], line 3 of the disclosure.

Applicant has provided a substitute Table 1 with an amended Title to reflect the correct spelling of the word "functional". Applicant has also corrected the spelling of the word tetracycline in paragraph [0048] on page 19.

Based on the foregoing amendments, Applicant requests withdrawal of the objection.

Rejection under 35 U.S.C. §112, second paragraph

A. Regarding the term "derivative"

The Examiner has rejected claims 9, 26, 44 and 59 under 35 U.S.C. §112, second paragraph as being indefinite. In particular, the Examiner alleges that the term "derivative" of present claims 9, 26, 44 and 59 is a relative term that renders the claims indefinite. More particularly, the term "derivative" does not particularly point out the degree or type of derivation that a given compound may have in relation to the parent compound and still be considered a derivative as intended by Applicant. The Examiner alleges that Applicant has provided no specific definition for this term in the present specification. Lacking a clear meaning of the term "derivative", the Examiner alleges that

the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter for which Applicant seeks patent protection.

Applicant respectfully traverses the Examiner's rejection and has amended the claims to delete reference to the term "derivative". The claims now recite "any tetracycline that crosses the blood brain barrier". Applicant asserts that one of skill in the art would be able to understand and ascertain the limitations of the claims, as currently amended. Withdrawal of the rejection is respectfully requested.

B. Regarding the phrase "related retrogenic degenerative neurological conditions"

The Examiner has rejected claims 8-9, 11-14, 43-44 and 46-49 as being indefinite. In particular, the Examiner alleges that the phrase "related retrogenic degenerative neurological conditions" is a phrase that renders the claims indefinite. The Examiner alleges that the corresponding disclosure does not point out the degree or type of relationship that a given retrogenic degenerative condition may have to those that are presently claimed (AAMI, MCI, CVD or AD) and still be considered a "related retrogenic degenerative neurological condition". Furthermore, Applicant has not provided any specific definition for this phrase in the present specification. Accordingly, the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter for which patent protection is desired. Moreover, the Examiner notes that the term "related retrogenic diseases" is defined as neurological conditions that present some degree of degeneration from the normal adult neurological condition. This includes measurable decline of normal cognitive, neurologic, or functional capacity.

As stated in the present application, in paragraph [0033], "The relationship between normal human development and AD has been termed "retrogenesis", and is defined as a process by which degenerative biological mechanisms reverse the order of acquisition of the same mechanisms in normal development." The application lists in table 1 the "levels of functional loss in Alzheimer's disease (AD) with corresponding developmental ages (DA) of functional acquisition" (page 8 of application). Accordingly, a retrogenic dementia can be defined as a dementia which follows this characteristic retrogenic functional clinical course in terms of sequence of loss of functional capacity.

Further in paragraph [0033], the retrogenic process "is also related to recent findings regarding the molecular biology of normal cellular development and the changes in these normal molecular processes in AD, CVD and other retrogenic dementias" (Reisberg et al., 2002, American Journal of Alzheimer's Disease, 17:202-212, EXHIBIT A), is cited at this point in the application. This reference teaches that, "The major apparent mechanism for the retrogenic phenomenon in AD and related dementing disorders has recently been elucidated." Activation of "mitogenic molecular markers including the mitogen-activated protein kinase (MAPK) cascade, cyclins, and cyclin dependent kinases" has been "related to the phosphorylation and hyperphosphorylation of tau, and, consequently, the development of neurofibrillary changes in AD" (Reisberg et al., 2002; page 205). Therefore, the retrogenic dementias also include the category of dementias known as the tauopathies.

Based on the foregoing, Applicant respectfully traverses the Examiner's rejection and have amended the claims to recite "related retrogenic diseases" and asserts that given the definition for this term in the present application, as noted by the Examiner and as summarized above, one of skill in the art is capable of ascertaining what cognitive or neurologic diseases fall within the meaning of this term, and moreover, which diseases would be considered a "related retrogenic disease" as currently defined in the present specification. It is to be understood that as defined, a retrogenic disease is one that includes a measurable decline of normal cognitive, neurologic or functional capacity. Further support for the definition of this term may be found in the reference supplied as Exhibit A, which is an article published in the American Journal of Alzheimer's Disease and Other Dementias, (Vol. 17, Number 4, July/August 2002) by the inventor of the present application, entitled: "Evidence and Mechanisms of Retrogenesis in Alzheimer's and Other Dementias: Management and Treatment Import". Based on the amendment to the claims, withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102(b)

The Examiner has rejected claims 8-9, 11, 13, 43-44, 46, 48, 56-60 and 62 under 35 U.S.C. §102(b) as being anticipated by Duncan (WO 02/020022 A1; March, 2002).

The Examiner alleges that Duncan teaches the administration of a tetracycline compound, such as minocycline, doxycycline or any tetracycline compound of the

formula (I) in an effective amount for the treatment of neurologic disorders, such as Alzheimer's disease, in an effective amount sufficient to down-regulate microglia expression, activation and production. The Examiner further alleges that Duncan teaches that the tetracycline compound may be administered with an agent capable of inhibiting inflammation in tissue, e.g. steroidal or non-steroidal anti-inflammatory drugs.

The Examiner has noted that present claims 8 and 43 require at least one first agent capable of inhibiting neuronal cell cycle progression at or before an early phase, at least one second agent capable of inhibiting neuronal cell cycle progression generally and optionally at least one third agent capable of inhibiting mitogenic stimulation. However, the Examiner notes that absent express disclosure by Applicant stating that the at least one first agent cannot be the same as the at least one second agent, the Examiner considers the use of minocycline or a tetracycline compound as taught by Duncan to meet both the limitation of (i) at least one first agent capable of inhibiting neuronal cell cycle progression at or before an early phase and (ii) at least one second agent capable of inhibiting neuronal cell cycle progression.

Furthermore, the Examiner alleges that regardless of whether minocycline or a tetracycline compound inhibits neuronal cell cycle progression selectively at or before an early phase or simply "generally" as Applicant has stated in claims 8 and 43, the Examiner alleges that the therapeutic endpoint is still the same, i.e., the inhibition of neuronal cell cycle progression, irrespective of what point in the cell cycle the compound actually inhibits progression. Such is further support that the at least one first agent and the at least one second agent are not required to be distinct from one another. Thus, for the purposes of examination, the Examiner has interpreted the limitations to the at least one first agent and the at least one second agent to be met by Duncan, who discloses the use of minocycline or a tetracycline compound.

In addition, while the Examiner had noted the recitation of the limitation "wherein the at least one first agent inhibits cell cycle progression...and/or reducing activated microlia-induced mitogenic stimulation" in present claim 57 (see lines 1-4) and the limitation "wherein the at least one first agent inhibits cell cycle progression at or prior to entry of a neuronal cell...and/or reducing activated microlia-induced mitogenic stimulation" in present claim 58 (see lines 1-4), the Examiner notes that such limitations

are considered a functional limitation of the agents, and, thus, fail to further limit the claimed method. Nevertheless, the Examiner alleges that because the claimed active agents are also taught by the prior art of Duncan for the same therapeutic purposes, there is no reason to doubt that the agents of the patent publication do not selectively act on cells in the S or G1 phase or that they are capable of inhibiting glutamate-induced excitotoxicity and/or reducing activated microlial-induced mitogenic stimulation, absent factual evidence to the contrary.

Lastly, the Examiner notes that while Alzheimer's disease is not expressly recited in present claim 8, absent factual evidence to the contrary, and absent any limiting definition provided by Applicant, the Examiner considers such a condition to meet Applicant's limitation of a "related retrogenic degenerative neurological condition".

Applicant's Position Regarding Duncan

Applicant respectfully traverses the Examiner's rejection and asserts that in order for a rejection under 35 U.S.C. §102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed.

Applicant asserts that Duncan teaches the use of tetracyclines for treating Alzheimer's disease, Guillain Barre syndrome, adrenoleukodystrophy, Parkinson's disease and amyotrophic lateral sclerosis. Moreover, tetracyclines were used for their anti-inflammatory properties, either alone or in conjunction with another anti-inflammatory compound.

The Examiner notes that Duncan does not teach the use of an inhibitor of glutamate excitotoxicity, such as memantine, nor does Duncan teach the use of salicylates as an anti-inflammatory agent, and furthermore, Duncan does not teach the treatment of age-associated memory impairment, mild cognitive impairment, or cerebrovascular dementia. Applicant is in agreement with the Examiner on these points and thus asserts that Duncan does not teach the methods of the present invention as currently claimed. Furthermore, given the current amendments to the claims, there are now further distinct differences between the teachings of Duncan and the present application.

For example, claim 8, as currently amended recites:

"A method of treating age associated memory impairment (AAMI), mild cognitive impairment (MCI), cerebrovascular dementia (CVD) and related retrogenic diseases, comprising administering a therapeutically effective amount of:

i) at least one first agent capable of inhibiting neuronal cell cycle progression;

ii) at least one second agent capable of inhibiting activated microglial-induced mitogenic stimulation, wherein the at least one second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAIDS), a salicylate, a steroid and an immunophillin; and

iii) at least one third agent capable of inhibiting glutamate-induced cytotoxicity, wherein the at least one third agent is selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrorphan, phencyclidine, and dexanabinol (HU-211)."

It is Applicant's position that Duncan did not appreciate the complexity of the retrogenic diseases for which the methods of treatment are disclosed in the present application. Nor did Duncan contemplate the use of three agents having different modes of action for treating patients having such retrogenic diseases, in particular, AAMI, MCI and cerebrovascular dementia. In fact, it was only through the work of the present inventor that these treatment strategies have been taught.

Applicant asserts that while the first agent of the present invention is an agent that prevents neuronal cell cycle progression, and that tetracyclines have been shown to inhibit neuronal cell cycle progression, Applicant believes that the use of a combination of therapies may prove more beneficial in treating a retrogenic disease, such as those presently disclosed and claimed. More importantly, the combination of a first agent that inhibits neuronal cell cycle progression with a second agent that is an anti-inflammatory agent and a third agent that inhibits glutamate cytoxicity, such as memantine, is not taught or suggested by Duncan. Moreover, Duncan does not teach or suggest the use of this combination of agents for treating age-associated memory impairment (AAMI), mild cognitive impairment (MCI) or cerebrovascular dementia.

In light of the foregoing claim amendments, Applicant respectfully requests withdrawal of the rejection.

Rejection under 35 U.S.C. §103(a)

Claims 8-9, 11-14, 23-30, 43-44, 46-49 and 56-63 are rejected under 35 U.S.C. §103(a) as being unpatentable over Duncan as applied to claims 8-9, 11, 13, 43-44, 46, 48,56-60 and 62 for the reasons made of record above, and further in view of Lipton (WO 92/17168: 1992), Lee, *et al.* (U.S. Patent No. 6,043,224; 2000) and Gervais, et al. (U.S. Patent Application Publication 2005/0031651; 2005, priority to U.S. Provisional Application 60/482,214 filed June, 2003).

The Examiner notes that the differences between the Duncan reference and the presently claimed subject matter lie in that the reference does not teach:

(i) the use of memantine as an inhibitor of glutamate-induced excitotoxicity;

(ii) the use of salicylates as the anti-inflammatory agent; and

(iii) the treatment of age-associated memory impairment, mild cognitive impairment, or cerebrovascular dementia.

However, the Examiner alleges that the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because of the following:

(i) It is acknowledged that Duncan is silent as to the use of the disclosed composition (i.e., comprising minocycline (or a tetracycline compound) and an anti-inflammatory agent) in further combination with memantine, an inhibitor of glutamate-induced excitotoxicity. However, the Examiner alleges that it was well known in the art that memantine was useful for the same therapeutic purpose of treating Alzheimer's disease by reducing neuronal damage by blocking NMDA receptor-operated channel activation by excitatory amino acids, such as glutamate-related compounds, when administered in an amount sufficient to block glutamates' effect on the NMDA receptor (see Lipton, et al., page 4, lines 23-31, page 10, lines 14-17 and page 10, line 32, page 11, line 3). According to the Examiner, it would, therefore, have been obvious to a person of

ordinary skill in the art to employ memantine in combination with the composition disclosed by Duncan because each was known in the art to be successful for achieving the same therapeutic effect. The Examiner further alleges that the motivation to administer both compounds flows logically from the efficacy of each compound in treating Alzheimer's disease and other neurodegenerative diseases as demonstrated in the prior art and also because each compound has been previously administered for the same therapeutic endpoints. The Examiner alleges that in the absence of evidence to the contrary, it is generally *prima facie* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ1069 (CCPA).

(ii) Although Duncan broadly teaches the use of an anti-inflammatory agent, both steroidal and non-steroidal, in combination with minocycline or a tetracycline compound, the reference is silent as to the particular use of salicylates as the anti-inflammatory compound. However, the Examiner alleges that the use of salicylates in compositions effective for the treatment of neurodegenerative diseases, such as Alzheimer's disease, was well known in the art at the time of the invention. Lee, *et al.*, teaches compositions of non-steroidal anti-inflammatory agents, such as aspirin or salicylic acid or the salicylates Asacol, Disalcid, Pentesa, Salflex or Trilisate, for the treatment of Alzheimer's disease and other neurodegenerative diseases (col. 5, lines 10-16; col. 10, lines 38-42 and col. 18, lines 25-58). The Examiner thus alleges that it would therefore, have been obvious to a person of ordinary skill in the art to employ any one or more of these known salicylate-type non-steroidal anti-inflammatory agents in the composition disclosed by Duncan because each would have been reasonably expected to exert the same inflammation-reducing effects as those required by the reference.

(iii) Although the previously cited references are silent as to the treatment of conditions such as age-associated memory impairment, mild cognitive impairment or cerebrovascular dementia, such conditions were known in the art to be related to the peptide amyloid-β, as taught by Gervais, *et al.* (U.S. Patent Application Publication 2005/0031651; page 3, paragraph [0024]). In light of the fact that Duncan expressly

teaches the minocycline (or a tetracycline compound)/anti-inflammatory composition useful for the treatment of Alzheimer's disease, which he expressly states is characterized by amyloid plaques associated with upregulated microglial cell expression (see page 1, line 28, - page 2, line 2 and 23-24) and that memantine is also useful for the same therapeutic objective of treating Alzheimer's disease, the Examiner alleges that it would have been appreciated by the skilled artisan that such a combination of agents would have been useful in the treatment of other disorders associated with the amyloid peptide, such as age-associated memory impairment (synonymous with age-related cognitive decline), mild cognitive impairment or cerebrovascular dementia. Such a person would have been motivated to treat such conditions with this combination of agents because it would have been reasonable expected that such a combination would demonstrate the same or a similar level of efficacy against other amyloid peptide related diseases as it would against the treatment of Alzheimer's disease.

Moreover, age-associated memory impairment and mild cognitive impairment are further considered by the examiner to be progressive conditions that precede the development of mature Alzheimer's disease. Thus, because such a combination would have efficacy in treating the advanced condition of Alzheimer's disease, the Examiner asserts that it would also be reasonably expected that the same combination of agents would have efficacy in treating the less severe conditions directly associated to and preceding the development of advanced Alzheimer's.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

The Invention as Claimed

The present invention, as currently claimed, teaches the use of a combination of three types of agents for treating retrogenic diseases, in particular, age-associated memory impairment (AAMI), mild cognitive impairment (MCI) and cerebrovascular dementia. More importantly, the present invention teaches that the first class of agents inhibits neuronal cell cycle progression, and these may be selected from the group consisting of minocycline, any tetracycline capable of crossing the blood brain barrier, acetylsalicylic acid, any salicylate which inhibits early phase cell cycle progression, sirolimus, any sirolimus derivative capable of inhibitng early cell cycle progression, flavopiridol, ciclopirox, a paulone, indirubin, fascaplycin, olomoucine, roscovitine, Aragusterol A, valproate, N-(3-chloro-7-indolyl)-1,4-benzenedisulfamide, a farnesyl transferase inhibitor such as R115777, SCH66336 and BMS-214662, and sodium butyrate. The second class of agents may be selected from agents that inhibit activated microglial-induced mitogenic stimulation, wherein the at least one second agent is an anti-inflammatory agent selected from the group consisting of a non-steroidal anti-inflammatory agent (NSAIDS), a salicylate, a steroid and an immunophillin. The third agent is an inhibitor of glutamate induced excitotoxicity, and the agent may be selected from the group consisting of memantine, neramexane, amantadine, riluzole, MK801, ketamine, dextromethorphan, dextrorphan, phencyclidine, and dexanabinol (HU-211).

The Duncan Reference

Applicant asserts that Duncan teaches the use of tetracyclines for treating neurological conditions such as Alzheimer's disease, Guillain Barre syndrome, adrenoleukodystrophy, Parkinson's disease and amyotrophic lateral sclerosis. Moreover, tetracyclines were used for their anti-inflammatory properties, either alone or in conjunction with another anti-inflammatory compound.

As noted by the Examiner, Duncan does not teach or suggest the use of an inhibitor of glutamate excitotoxicity, such as memantine. Nor does Duncan teach or suggest the use of a salicylate as the anti-inflammatory agent. Furthermore, Duncan does not teach the treatment of AAMI, MCI or cerebrovascular dementia.

Applicant asserts that Duncan does not teach or suggest the use of a composition comprising at least one first agent that is an inhibitor of neuronal cell cycle progression, such as tetracycline, combined with at least one second agent, such as an anti-inflammatory, combined with a third agent, such as an inhibitor of glutamate induced excitotoxicity, all as described in the present application, for the treatment of AAMI, MCI or cerebrovascular dementia.

The Lee et al. Reference

Lee et al. teach the use of compositions of non-steroidal anti-inflammatory agents, such as aspirin, or salicylic acid, or the salicylates Asacol, Disalcid, Pentesa, Salfex or Trilisate for the treatment of Alzheimer's disease.

Lee et al. do not teach or suggest the use of a composition comprising at least one first agent that is an inhibitor of neuronal cell cycle progression, such as tetracycline, combined with at least one second agent, such as an anti-inflammatory, combined with a third agent, such as an inhibitor of glutamate induced excitotoxicity, all as described in the present application, for the treatment of AAMI, MCI or cerebrovascular dementia.

The Lipton Reference

Lipton teaches the use of compositions containing NMDA receptor antagonists to treat neurodegenerative diseases. In particular, Lipton teaches the use of compounds including amantadine, rimantadine and memantine to treat hypoxia-ischemic encephalopathy, seizures, stroke, and AIDS dementia.

Lipton does not teach or suggest the use of a composition comprising at least one first agent that is an inhibitor of neuronal cell cycle progression, such as tetracycline, combined with at least one second agent, such as an anti-inflammatory, combined with a third agent, such as an inhibitor of glutamate induced excitotoxicity, all as described in the present application, for the treatment of AAMI, MCI or cerebrovascular dementia. In addition, Applicant asserts that the use of memantine for treating moderate to severe Alzheimer's disease was not approved by the FDA until September, 2003, following a study conducted by the present inventor, the results of which were not published until after the priority date of the present application. The article summarizing this study can

be found attached herewith as EXHIBIT K (New England Journal of Medicine April 3, 2003, pages 1333-1341).

The Gervais et al. Reference

Gervais et al. teach a method of concomitant therapy for patients suffering from diseases associated with enhanced beta amyloid peptide. The therapy includes the use of two agents, one being an agent that either blocks beta amyloid toxicity, or prevents or slows the rate of beta-amyloid formation. The second agent may be an anti-inflammatory agent or an acetyl cholinesterase inhibitor, or an agent that further prevents beta amyloid formation. Other neuroprotective second agents are also disclosed.

Gervais et al. do not teach or suggest the use of a composition comprising at least one first agent that is an inhibitor of neuronal cell cycle progression, such as tetracycline, combined with at least one second agent, such as an anti-inflammatory, combined with a third agent, such as an inhibitor of glutamate induced excitotoxicity, all as described in the present application, for the treatment of AAMI, MCI or cerebrovascular dementia.

The analysis under § 103(a).

Applicant asserts that the teachings of Duncan, when combined with the teachings of Lee, Lipton and Gervais do not teach or suggest the aspects of the present invention, as currently claimed. Moreover, it is Applicant's contention that one of skill in the art would not have been motivated to combine the teachings of Duncan with those of Lee, Lipton, and Gervais to result in the teachings of the present invention. Moreover, it is also Applicant's contention that, based on certain teachings in the art, as noted below, there would be no reasonable expectation of success if one were to combine the teachings of Duncan with those of Lee, Lipton, and Gervais.

While the Examiner alleges that absent express disclosure by Applicant stating that the at least one first agent cannot be the same as the at least one second agent, the Examiner considers the use of minocycline or a tetracycline compound as taught by Duncan to meet both the limitation of (i) at least one first agent capable of inhibiting neuronal cell cycle progression at or before an early phase and (ii) at least one second agent capable of inhibiting neuronal cell cycle progression. Applicant asserts that while the present application does not expressly state that the first and second agent cannot be

the same agent, in particular, a tetracycline, Applicant further asserts that the differences between the first and second agent, as currently claimed, is inherent in the teachings throughout the specification and the claims as filed.

As noted in the present application, (paragraphs [0049], [0050] and especially [0051] to [0053]) minocycline and other tetracycline family compounds are disclosed for use in treating AAMI, MCI and cerebrovascular dementia based on their cell cycle inhibitory effects and more particularly for their effects on early phase cell cycle progression.

Applicant notes in the application in paragraph [0051] that:

"These effects on the cell cycle likely account in part for other observed effects of minocycline including the recently uncovered effects on cerebral ischemia and inflammation (Yrjänheikki, et al. (1999) Proc. Natl. Acad. Sci. USA 96: 13496 – 13500; Yrjänheikki, et al. (1998) Proc. Natl. Acad. Sci. USA 95: 15769 – 15774)."

Duncan refers to prior art and knowledge regarding the hypothesis that anti-inflammatory treatment may be useful in Alzheimer's disease. Duncan notes that "One proposed therapeutic approach is to minimize or prevent the inflammatory changes that occur in the brains of, e.g., Alzheimer's patients (Selkoe 1999). It is thought that a key cell in the cellular cascade that results in neuronal death in Alzheimer's disease is the microglial cell." He also notes that in the prior art "It has been reported that minocycline, a tetracycline compound, reduced the microglial response in the area surrounding areas of brain ischemia in an experimental model of stroke, and that it protects neurons against death in tissue culture (Yrjänheikki, et al. 1999, 1998)."

The present application once again differs markedly from Duncan in that the present application suggests the utility of minocycline and related tetracycline compounds because of cell cycle events, not anti-inflammatory effects. Therefore, the dosage, endpoint and goal of administration are very different from those proposed by Duncan who suggests, "a method of providing ...an effective amount of a tetracycline compound sufficient to down regulate microglial expression, activation and production, and hence, prevent, reduce or minimize inflammation" (p.2, Duncan).

<u>Regarding the Use of Anti-inflammatories eg. salicylates, for Treating Alzheimer's Disease</u>

Applicant respectfully traverses the Examiner's allegations that it would be obvious to combine the teachings of Duncan on the use of tetracycline in combination with an anti-

inflammatory such as a salicylate, because it is known in the art that salicylates are useful for treating Alzheimer's disease. Applicant asserts that in fact, the anti-inflammatory approach to the treatment of Alzheimer's disease has not been successful as a first approach, which is in disagreement with the Examiner's allegations. For example, Aisen et al., found that the anti-inflammatory medications rofecoxib and naproxen do "not slow cognitive decline in patients with mild to moderate AD" (Aisen et al., 2003, EXHIBIT B). In another study of patients with mild cognitive impairment Thal et al. found that, "The results from this MCI study did not support the hypothesis that rofecoxib would delay a diagnosis of AD" (Thal et al., 2005, EXHIBIT C). Accordingly, no anti-inflammatory compounds have been approved by the FDA or other regulatory agencies for the treatment of AD, MCI, AAMI, cerebrovascular dementia or other retrogenic dementias.

Furthermore, the present application does not claim an anti-inflammatory agent as a first agent in the treatment of Alzheimer's disease (AD) or other named therapeutic entities. Accordingly, the present application is clearly different from the teachings of Duncan.

Regarding AAMI and MCI to be Progressive Conditions Leading to Alzheimer's Disease

In addition, the Examiner states (p.17), that "age associated memory impairment and mild cognitive impairment are further considered by the examiner to be progressive conditions that precede the development of mature Alzheimer's disease. Thus, because such a combination would have efficacy in treating the advanced condition of Alzheimer's disease, it would also reasonably be expected that the same combination agents would have efficacy in treating the less severe conditions directly associated to and preceding the development of advanced Alzheimer's."

The Applicant respectfully differs on each of these matters on the basis of current literature and knowledge. As noted by Wang et al., (EXHIBIT D), (2004) "it is unknown whether, and to what extent, self perceived decline is a perception of the normal aging process or might represent an early sign of dementia." Wang et al. note that most of the population based longitudinal studies have "included individuals with objective cognitive impairment and therefore were unable to address the question of whether subjective memory complaints were a sign of future dementia at an early stage when objective impairment was not evident."

Mild cognitive impairment (MCI) is also a condition which does not necessarily progress to frank dementia, nor does it necessarily progress to Alzheimer's disease. In the present application,

Applicant notes evidence from the work which the inventor has done which indicates that cell cycle inhibitors may nevertheless be useful in the treatment of this condition. For example, Roach, (EXHIBIT E), (2005) quotes Gauthier and Touchon as stating that "although individuals with MCI have an increased likelihood of progressing to frank dementia during a 10 years interval many of them remain stable and some even revert to normal during this period" (Gauthier, Touchon 2005, EXHIBIT F).

Regarding the Assumption that Medications Useful in Alzheimer's Disease are Effective in Treating Other Retrogenic Diseases or Conditions

It should also be noted that there is universal agreement that medications which are effective for Alzheimer's disease are not necessarily effective for MCI. Clearly, there is also universal agreement throughout the field that medications which are effective for Alzheimer's disease are not necessarily, or even likely, to be effective for AAMI.

Even within the restricted range of Alzheimer's disease, all of the medications which have been approved by the U.S. Food and Drug Administration have been approved for either treatment of mild to moderate Alzheimer's disease exclusively, or, alternatively, moderate to severe Alzheimer's disease exclusively. Furthermore, none of these medications are approved for treatment of mild cognitive impairment. In fact, despite studies in the mild cognitive impairment area, no medications have been approved at this time for the treatment of either mild cognitive impairment or age associated memory impairment.

More specifically, the cholinesterase inhibitors, donepezil, rivastigmine and galantamine have been approved exclusively for the treatment of mild to moderate Alzheimer's disease (Physicians' Desk Reference, pages 1197-1200; 2304- 2311;1736- 1741 respectively, 2005, Thomson PDR). This limited approval obviously speaks volumes for the FDA's belief that a medication approved for a specific severity range, even within the Alzheimer's disease diagnosis, does not necessarily mean that the medication is effective for other severity ranges and certainly not for other diagnoses.

Memantine, an NMDA receptor antagonist, has been approved by the FDA for the treatment of moderate to severe Alzheimer's disease (Physicians' Desk Reference, pages 1288-1291, 2005, Thomson PDR, EXHIBIT G). There has been an effort on the part of the clinical scientist to extend memantine's approval to the range of mild Alzheimer's disease. Recently, the

FDA rejected memantine for approval for the treatment of mild Alzheimer's disease (FDA rejects memantine for mild Alzheimer's, Alzheimer's Association 2005, EXHIBIT H).

There has been an effort to examine the efficacy of cholinesterase inhibitors in the treatment of mild cognitive impairment. Thus far, it is not clear whether any of them are effective in this disease entity. For example, Salloway et al. studied the efficacy of donepezil in a randomized placebo-controlled trial in mild cognitive impairment (Salloway et al., 2004, EXHIBIT I). They concluded that "significant treatment effects were not seen in the primary efficacy measures." However, they also concluded that, "outcome on secondary measures suggest promising directions for further evaluation of donepezil treatment in patients with MCI." (Salloway et al., Neurology 2004; 63:651-657, EXHIBIT I, quotes from the abstract page 651). Other current studies of cholinesterase inhibitors to date have either been negative or inconclusive.

Regarding the Obviousness to Combine Two Agents

The examiner also implies that if one medication is approved for an indication and another medication is also approved for that same indication, then naturally, it is obvious to everyone that both medications are better than one medication alone for that indication. Aside from errors in syllogistic logic, this reasoning in fact does not apply to Alzheimer's disease specifically, nor should it preclude patentability of the present invention. For example, if one prescribes a cholinesterase inhibitor for treating Alzheimer's disease, such as donepezil, adding another cholinesterase inhibitor does not increase efficacy. Such a procedure does however increase the potential for side effects. The reason for this is that there is a window of treatment efficacy for cholinesterase inhibitors in the approved mild to moderate Alzheimer's disease treatment range. If one exceeds this window then there is an excess of cholinergic side effects and not an increase in efficacy.

There has been one study of combining the two classes of AD treatments and examining efficacy and side effects. This study in patients with moderate to severe AD receiving stable doses of donepezil, a cholinesterase inhibitor found that memantine treatment "resulted in significantly better outcomes than placebo." The conclusion of the study was that, "these results, together with previous studies, suggest that memantine represents a new approach for the treatment of patients with moderate to severe AD" (Tariot et al., JAMA 2004; 291: 317-324, EXHIBIT J, quotes from abstract, page 317). This study did not indicate whether the combination of cholinesterase inhibitor

treatment with memantine (NMDA receptor blocker) treatment was better than either substance alone in the severity range of the study.

There is some evidence that the combination of a cholinesterase inhibitor treatment with NMDA receptor antagonism treatment may not be additive. This study suggests that both treatment modalities for Alzheimer's disease may be acting on a common disease mechanism. Specifically, De Sarno et al., in press, conclude that, "drugs in each class of therapeutic agents used for AD have the common property of increasing the regulatory serine-phosphorylation of GSK-3 within common pools of the enzyme" (De Sarno et al., Neurobiology of Aging, in press).

In the present application, Applicant proposes combinations of treatments which would have synergistic efficacy, based on Applicant's model of retrogenesis and cell cycle inhibition.

Accordingly, Applicant asserts that it is not obvious to combine the three treatment modalities of the present application for the reasons cited above.

Regarding Amyloid and Alzheimer's disease:

The relationship between amyloid and Alzheimer's disease is unclear at the present time. There are many who believe that the amyloid is a "scar" of the disease and does not have any particular causal relationship to AD. In the case of injury to the body, scar tissue may form. This association does not mean that the scar caused the injury. Similarly, there seems to be some association between the presence of amyloid (an amorphous proteinaceous material, comprised in part of a protein product known as beta amyloid [Aβ], which contains varying numbers of amino acids, e.g., either 40 or 42 amino acids) and the occurrence of Alzheimer's disease. However, "the number of Aβ aggregates in the brain doesn't always correlate with the severity of dementia" (Anderson, M.W., The Scientist, October 25, 2004, pages 28-29). Indeed studies of the cerebrospinal fluid (CSF) have indicated either no change in Aβ peptides or a reduction. Specifically, there is a "reduction in CSF Aβ 42" however, "there is no change in CSF Aβ 40 in AD" (Hampel and Blennow, CSF tau and beta amyloid as biomarkers for mild cognitive impairment, Dialogues in Clinical Neuroscience, 2004, Vol. 6, No.4, pages 379-390, quote from page 383). Naturally, if Aβ is related to AD one would expect an increase in the CSF content of this substance rather than what is observed, namely, no change or a reduction. There are various speculations as to possible reasons for the observed findings.

The Examiner's attention is drawn to the fact that no treatments for Alzheimer's disease based on lowering, raising, or otherwise changing beta amyloid, or any other element of amyloid plaques, have been approved in the U.S. or anywhere else at the present time.

Regarding Amyloid and MCI

Studies of the relationship between the diagnosis of mild cognitive impairment (MCI) and Aβ have been inconsistent. For example, in the CSF studies, "one study found significant decrease in the CSF Aβ1-42 in MCI subjects compared with controls. In another study in MCI patients who eventually developed AD, however, Aβ1-42 levels did not differ significantly from age matched controls." (Hampel and Blennow, CSF tau and beta amyloid as biomarkers for mild cognitive impairment, Dialogues in Clinical Neuroscience, 2004, Vol. 6, No.4, pages 379-390, quote from page 383). Again, intuitively, one would expect an increase in Aβ CSF levels, if there were a direct causal relationship between beta amyloid and MCI. However, what is observed is no change or a decrease.

The Examiner's attention is drawn to the fact that no treatments for MCI based on lowering, raising, or otherwise changing beta amyloid, or any other element of amyloid plaques, have been approved in the U.S. or anywhere else at the present time.

Aging is believed to be associated with an increase in beta amyloid plaques in the brain. Little or nothing is presently known regarding the association between beta amyloid and AAMI.

The Examiner's attention is drawn to the fact that no treatments for AAMI based on lowering, raising, or otherwise changing beta amyloid, or any other element of amyloid plaques, have been approved in the U.S. or anywhere else at the present time.

The relationship between vascular dementia treatment and treatment of Alzheimer's disease.

The Examiner states that it is obvious that if a treatment is useful for Alzheimer's disease then it should be useful for vascular dementia. Logically, of course, this is not necessarily true. The literature also does not support this conclusion. For example, a prevention study of non steroidal anti-inflammatory drugs (NSAIDs) found that, "the long term use of NSAIDs may protect against Alzheimer's disease but not against vascular dementia" (Veld, et al., NEJM, 2001; Vol. 345:1515-21, quote from abstract page 1515).

The relationship between a medication which prevents an illness and a medication which treats the illness.

The examiner implies that a medication which treats an illness such as Alzheimer's disease is likely to be useful in preventing the condition.

Applicant respectfully asserts that this is not true. For example, in Alzheimer's disease, five medications have been approved for treatment in the U.S. None of these medications have been approved for preventing Alzheimer's disease. The same is true for other conditions. For example, another brain disease is schizophrenia. Many medications have been approved for the treatment of schizophrenia, but none of these medications have been approved for the prevention of schizophrenia.

Based on the foregoing, Applicant asserts that the present invention is still patentable over Duncan in view of Lee, Lipton and Gervais for at least the following reasons:

1. There simply is no teaching or suggestion to use a combination of three agents, one being a cell cycle inhibitor, one being an anti-inflammatory and the third being an NMDA antagonist, having the noted characteristics as currently claimed, for treating a retrogenic disease.
2. There simply is no teaching or suggestion to use a combination of three agents, one being a cell cycle inhibitor, one being an anti-inflammatory and the third being an NMDA antagonist, having the noted characteristics as currently claimed for treating AAMI, MCI and cerebrovascular dementia.

Based on the foregoing, withdrawal of the rejection is respectfully requested.

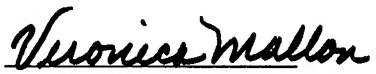
Fees

A check in the amount of $325. is enclosed to cover the fee for three new independent claims and one new dependent claim over 20. No other fees are believed to be necessitated by the foregoing response. However, if this is in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusion

Applicants believe that the foregoing cancellation and amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,



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Attachments: References listed as EXHIBITS A THROUGH K

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Evidence and mechanisms of retrogenesis in Alzheimer's and other dementias: Management and treatment import

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Abstract

Retrogenesis is the process by which degenerative mechanisms reverse the order of acquisition in normal development. Alzheimer's disease (AD) and related conditions in the senium have long been noted to resemble "a return to childhood." Previously, we noted that the functional stages of AD precisely and remarkably recapitulated the acquisition of the same functional landmarks in normal human development. Subsequent work indicated that this developmental recapitulation also applied to the cognitive and related symptoms in AD. Remarkably, further investigations revealed that the same neurologic "infantile" reflexes, which mark the emergence from infancy in normal development, are equally robust indicators of corresponding stages in AD. Neuropathologic and biomolecular mechanisms for these retrogenic processes are now evident. For example, the pattern of myelin loss in AD appears to mirror the pattern of myelin acquisition in normal development. Also, recent findings indicate that mitogenic factors become reactivated in AD, and, consequently, the most actively "growing" brain regions are the most vulnerable. Because of this robust retrogenic process, the stages of AD can be translated into corresponding developmental ages (DAs). These DAs can account for the overall management and care needs of AD patients. A science of AD management can be formulated on the basis of the DA of the Alzheimer's patient, taking into consideration differences of AD from normal development as well as homologies.

Key words: Alzheimer's disease, care concepts, dementia, dementia management, retrogenesis

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Historical background

Retrogenesis can be defined as the process by which degenerative mechanisms reverse the order of acquisition in normal development.[1] General relationships

between aging and development have long been noted by poets and playwrights,[2,3] and are incorporated in the vocabulary of the English and other languages. More than two centuries ago, physicians also began to note similarities between aging and normal infant-child development.[4] In the 1960s and 1970s, de Ajuriaguerra and associates observed that the decline of certain capacities in dementia appeared to reverse Piaget's developmental stages.[5-7]

Functional retrogenesis

Systematic empirical studies of the symptomatology of brain aging and progressive Alzheimer's disease (AD) in the 1980s resulted in the description of 16 successive functional stages and substages that were incorporated in the *functional assessment staging* (FAST) procedure.[8,9] Simultaneously, this functional progression was recognized as reversing the order of acquisition of the same functions in normal human development (Table 1).[10] Also immediately observed was that this functional progression was characteristic, but not pathognomonic, of the dementia of AD.[11,12]

One concern of subsequent research was validating this characteristic functional progression of AD. Strong correlations with existing dementia measures (*e.g.*, the Mini-Mental State Exam [MMSE][13]) were immediately apparent;[8] however, the final six to eight FAST substages occurred after the MMSE produced floor effects. Consequently, new measures needed to be developed for assessment of cognition in severe dementia, and the latter portion of the FAST had to be validated against these new measures. This was accomplished over the next decade.[14] Other investigations concerned the "criterion validity" of the FAST progression of AD. The FAST progression showed unprecedented strong relationships to neuropathologic post-mortem assessments of hippocampal volume loss,[15] cell loss,[16] and neurofibrillary changes[16] in AD. In another "criterion validity" study of the prospectively charted longitudinal course of AD, the FAST accounted for approximately twice the variance in temporal course of that explained by the MMSE.[17]

Consequently, these investigations indicated that:

- A characteristic functional course of AD was identifiable with the FAST staging procedure; and
- This characteristic course reversed normal human functional developmental acquisition.

Cognitive retrogenesis

The FAST staging procedure was developed from efforts to systematically describe optimally concordant ordinal assessments of progressive changes in AD.[18] These efforts, in turn, followed from the development of the Global Deterioration Scale (GDS).[19] One of the concordant ordinal assessments developed was *praxic capacity*.[20] Studies demonstrated that the evolution of praxic deficit in AD followed the retrogenic pattern.[21] Furthermore, if the FAST stages of AD and the corresponding praxis stages of loss in AD were each translated into corresponding developmental ages (DAs), *the loss of praxic capacity in AD occurred, on average, at the same DA as the loss of functional capacity.* In other words, cognitive retrogenesis in AD could be shown as concordantly mirroring functional retrogenesis.

Research from other centers also demonstrated the phenomenon of cognitive retrogenesis in AD. For example, a study of the MMSE, a measure developed for the assessment of cognition in AD and other dementias, was conducted in normal children. The investigators found an equally robust relationship between MMSE scores and mental age (MA), based on IQ scores in children, as has been observed between MMSE scores and any independent, objective dementia assessment in AD.[22]

We adapted a Piagetian test battery, the Uzgiris and Hunt Ordinal Scales of Psychological Development, for use in assessment of residual cognition in AD[23] and observed very strong relationships ($r = 0.8$) between the resulting measure (denoted M-OSPD) and FAST measurements of functional deterioration in AD.[14] Thornbury compared performance on Piagetian tasks by AD patients with MMSE scores and obtained a similar correlation (*i.e.*, $r = 0.8$) to that which we have noted with FAST scores and Piagetian measures.[24]

Therefore, we determined the following:

- Cognitive retrogenesis appears to be as robust as functional retrogenesis. Specifically, *dementia measures appear to be just as good at measuring normal human development as they are at measuring dementia. Conversely, infant-child developmental measures appear to be just as good at measuring dementia in AD as in measuring cognitive development;* and
- Cognitive retrogenesis appears to occur, from certain perspectives, concordantly with AD-based functional retrogenesis. It appears that *cognition and functioning are linked in the same intimate qualitative and quantitative relationship in dementia as they are in normal development.*

Emotional retrogenesis

Once the functional and cognitive landmarks of

Table 1. Functional landmarks in normal human development and Alzheimer's disease*

Normal development (approximate total duration: 20 years)

Approximate age		Approximate duration in development	Acquired abilities	Lost abilities	Alzheimer stage	Approximate duration in AD	Developmental age of patient
Adolescence	13 – 19 yrs	7 yrs	hold a job	hold a job	3 (incipient)	7 yrs	19 – 13 yrs (adolescence)
Late childhood	8 – 12 yrs	5 yrs	handle simple finances	handle simple finances	4 (mild)	2 yrs	12 – 8 yrs (late childhood)
Middle childhood	5 – 7 yrs	2½ yrs	select proper clothing	select proper clothing	5 (moderate)	1½ yrs	7 – 5 yrs (middle childhood)
Early childhood	5 yrs 4 yrs 4 yrs 3 – 4½ yrs 2 – 3 yrs	4 yrs	put on clothes unaided shower unaided toilet unaided control urine control bowels	put on clothes unaided shower unaided toilet unaided control urine control bowels	6a (moderately severe) b c d e	2½ yrs	5 – 2 yrs (early childhood)
Infancy	15 mo 1 yr 1 yr 6 – 10 mo 2 – 4 mo 1 – 3 mo	1½ yrs	speak 5 – 6 words speak 1 word walk sit up smile hold up head	speak 5 – 6 words speak 1 word walk sit up smile hold up head	7a (severe) b c d e f	7 yrs	15 mo – birth (infancy)

Alzheimer's degeneration (approximate total duration: 20 years)

degeneration in AD were established and the DAs corresponding to these landmarks were identified, other aspects of the retrogenic process could be studied. In a series of studies, we identified characteristic behavioral and psychological symptoms of dementia and the stages in the evolution of dementia at which these symptoms emerged.[25-37] Interestingly and importantly, many of these symptoms occurred at precisely the point that would be anticipated from the corresponding DA of the AD patient.[28,29]

Neurologic retrogenesis

Neurologic release signs, also referred to as primitive, developmental, or neonatal reflexes because of their occurrence in normal infancy, have long been known to occur in elderly persons and dementia patients.[30-33] Systematic studies precisely measured these reflexes and established the precise stages in the evolution of AD at which they emerged.[34-36] *These studies indicated that many of the same reflexes that are used to mark the emergence from normal infancy to early childhood appear to be equally robust markers of the emergence of the infantile DA stage of AD* (*i.e.*, movement from the end of FAST stage 6, into FAST stage 7).[36]

Neuropathologic retrogenesis

A neuropathologic pattern of degeneration in AD, which appeared to reverse the normal human developmental pattern, was first observed by Brun and Gustafson a quarter century ago.[37] Subsequently, at least three

neuropathologic pattern in AD in terms of neuronal cell loss,[38] neurometabolic change,[38] neurofibrillary change,[39] and myelin vulnerability.[39,40]

Biomolecular retrogenesis

The major apparent mechanism for the retrogenic phenomenon in AD and related dementing disorders has recently been elucidated. The response of the neuron to stressors, including beta-amyloid, is an attempt to regenerate.[41,42] The result of this mitogenic stimulus is the activation of various mitogenic molecular markers, including the mitogen-activated protein kinase (MAPK) cascade, cyclins, and cyclin-dependent kinases.[43-53] Activation of MAPK in the hippocampus has been shown to be linked to contextual and spatial memory formation in the hippocampus.[54-57] Activation of these factors in some cases appears to precede the development of neuronal neurofibrillary changes.[45,46] Some of these mitogenic factors have been related to the phosphorylation and hyperphosphorylation of tau, and, consequently, the development of neurofibrillary changes in AD.[43,58,59] Reactivation of mitogenic factors has also been related to apolipoprotein (APP) processing into amyloidogenic elements.[60]

Consequently, this biomolecular research in AD indicates that *the most metabolically active regions of the brain in AD, which are the most capable of responding to a mitogenic stimulus, are the most vulnerable in AD.*[48,49] These phenomena clearly appear to account for the neuropathologic, neurologic, cognitive, functional, and emotional retrogenic phenomena reviewed in the preceding sections.

Risk factors for dementia and retrogenesis: Arboreal entropy

Some AD and dementia pathogenic factors currently have been associated with mitogenic factor activation. These include hypoxia and beta-amyloid (1-42).[42] However, other risk factors for AD have, at this time, been related primarily to myelin disturbance. These include low vitamin B12 levels, folate deficiency, increased serum homocysteine levels, and increased serum methylmalonic acid levels.[61-63] Atherosclerosis and cerebrovascular disease are other risk factors associated with AD, which have been primarily associated with myelin disruption.[64-66]

Therefore, a full understanding of the retrogenic process in AD probably encompasses myelin as well as mitogenic neuronal reactivation. The process of myelination is now known to continue well into the latter portion of life. Neurons that are myelinated early in the life become Possibly, myelin plays a role not only in the conduction of electrical impulses in the neuron, but also in protection and maintenance of the oligodendroglial, myelin, and axonal relationship.[1,67] Consequently, the most recently affected, and, as a result, most thinly myelinated brain regions, may be the most vulnerable to injury.[67]

A terminology that appears to describe the pattern of neuronal vulnerability accounting for the retrogenic observations is *arboreal entropy*. Just as the bark of a tree protects it from external injury and, to some extent, the thicker the bark, the greater the protection, the myelin protects the axon and its neuron. Hence, to some extent, we may say the thicker the myelin, the greater the protection. However, just as a tree can also be attacked from the inside, which ultimately rots the bark, the axon can be attacked from the inside. For example, neurofibrillary changes and neurotubular changes, secondary to mitogenic factor activation and tau hyperphosphorylation, can result in axonal destruction and resultant myelin loss. Note that the myelin is a living, metabolically active part of the axon of the neuron, with a membrane running through it, which is an extension of the cell (axonal) membrane. As a metabolically active cellular component, myelin is vulnerable to cellular and axomal injury.

Retrogenesis in non-AD dementias

At present, it is clear that the biomolecular factors and myelin vulnerability factors, which produce the phenomenon of retrogenesis in AD, frequently operate in other dementia disorders as well.

For example, investigators who have studied the M-phase mitotic markers cyclin B1 and cdc 2 in diverse dementing disorders have found increased activity in a variety of dementias, including, in addition to AD, Down's syndrome, frontotemporal dementia linked to chromosome-17, amyotrophic lateral sclerosis (ALS) dementia complex of Guam, Niemann Pick disease type-C, progressive supranuclear palsy, corticobulbar degeneration, and Pick's disease.[53] A common feature in most of these dementias is the occurrence of hyperphosphorylated tau, although not in a form necessarily associated with AD type neurofibrillary tangles. In contrast, these investigators found little or no increased activity of these particular M-phase mitotic markers in Parkinson's disease (PD), Huntington's disease (HD), ALS, multiple sclerosis (MS), pituitary adenoma, AIDS dementia, and fungal infection.[53]

Also, conditions such as vitamin B12 deficiency and hyponatremia clearly can produce myelin disturbances that may result in dementing conditions.

The extent to which non-AD dementias show a retrogenic pattern of progressive clinical pathology is likely

dependent, in part, on the occurrence of retrogenic biomolecular and neuropathologic phenomena.

Management import of retrogenesis in AD

An understanding of the phenomenon of retrogenesis in AD permits the foundation of a new science of AD care.[29] This science is based on fundamental human needs, which apply to humans at all ages, and an understanding of the DA of the AD patient. Fundamental human needs include those for movement, socialization, love, and dignity. Typically, these fundamental needs are frequently not understood in the AD patient.

For example, in nursing homes in the United states, until recently, late-stage AD patients were routinely put into "geri-chairs," which prevented ambulation, to prevent falling. The situation would be analogous to locking infants in chairs to prevent falling. The AD patients commonly developed deformities, probably in large part because of their restricted movement.[68] Infants who were similarly restricted also would probably develop deformities.

To cite another example, although everyone knows infants need overt expressions of love, love is not frequently provided to AD patients. This is especially true of late-stage AD patients in nursing homes.

In many ways, the situation today is quite similar to the 18th century, when psychiatric patients were kept in chains and there was little understanding of mental illnesses. An understanding of retrogenesis provides a basis for more sophisticated principles of care.

A new science of AD care based on retrogenesis

The new science of AD care can be formulated into axioms, postulates, and caveats. *Axioms* in this context are self-evident basic human needs and desires, applicable at all ages. *Postulates* are testable hypotheses of AD patient care. Treatment, based on the postulates, is dependent on satisfaction of the axioms. *Caveats* are exceptions to the DA-retrogenesis model, based on the nature of human aging and AD. The science of AD management is the clinical science and art of AD patient care, based on the interaction of the axioms, postulates, and caveats.

Care axioms

Examples of the axioms of AD management include the following:

Axiom I: All human beings avoid trauma and humiliation. AD patients, at any stage, avoid or rebel against experiences that are perceived as humiliating. The most prominent humiliating experience for the AD patient is appearing "stupid." Therefore, even early in the disease process, patients may avoid being questioned. As the disease progresses, patients may resist the humiliation of requiring a caregiver. So-called "delusions," such as that people are stealing things, have a psychologic basis insofar as AD patients at these stages prefer to accuse others of taking things, rather than accept the humiliation of admitting to themselves or others that they cannot remember.

Axiom II: All human beings seek a sense of accomplishment. In early AD (GDS stage 4), this sense of accomplishment can come from continued productivity. For example, an artist may continue to paint. A lawyer may continue the pretense of working on cases. One judge had his daughter write opinions. GDS stage 5 patients may continue to insist that they are working, even if they have been forced to retire. Later in AD, a sense of accomplishment may come from folding towels and other simple DA-appropriate activities.

This axiom has important corollaries (*i.e.*, consequences or results which follow from the axiom), which are:

- All human beings resist losses;
- A sense of accomplishment can be fostered by beginning with what an AD patient can do and building upon this; and
- A sense of accomplishment comes from practicing an area of residual expertise or learning new things.

Axiom III: All human beings seek a sense of dignity and self-worth. This dignity and self-worth may come from practicing previously mastered skills. It may also come from optimal participation in "adult" activities. Or, it may also be fostered by introducing necessary caregivers as "friends." A corollary of this is that if an AD patient perceives an activity as "infantile" or "childish" and, therefore, as an affront to his or her dignity, they may become angry and refuse to participate.

Axiom IV: All human beings are social organisms. Therefore, the social needs of the AD patient remain throughout the illness process. Even in the late stage (GDS and FAST stage 7), patients continue to require interaction with caregivers and others for mental and physical health and well-being.

Axiom V: All human beings seek praise and acceptance. As social organisms, AD patients continue to require positive social reinforcement throughout the course of the illness process in order to maintain their motivation and skills.

learn. One aspect of this capacity to learn is that AD patients can be retrained in many of the skills they have lost by breaking the tasks down into small stages, which are achievable, and praising the patient for his or her accomplishments.

Axiom VII: All human beings require love. This is necessary for the emotional and physical health of the AD patient at all points in the illness process.

Axiom VIII: All human beings have the capacity for happiness if basic needs are fulfilled. This means that AD is a physiologically congruent process. As such, if proper care is provided and social, emotional, and other needs are met, AD patients need not suffer and they can derive satisfaction from their existence.

Axiom IX: All human beings have the need for physical movement. Indeed, movement is sometimes said to be a fundamental feature of animal life. As is the case of the other axioms, this fundamental need is frequently ignored or not recognized in AD patients to such an extent that, until recently, AD patients were routinely restrained in order to prevent falling. Naturally, this restraint actually increased falls in patients, who were made increasingly unstable from the restraints. Hence, the need for movement remains frequently unrecognized in the AD patient.

Axiom X: All human beings have the capacity to remember. As is true of many of the other axioms, this basic human capacity is frequently not recognized, particularly in the late-stage (GDS and FAST stage 7) AD patient. If the person's memory is placed in the context of the DA of the AD patient, his or her memory capacity becomes comprehensible and assessable. Just as a one-year-old child will forget people and events more quickly, a stage 7 AD patient will forget people and events more quickly than a healthy adult. Three weeks is a very long time for a stage 7 AD patient or a one-year-old child. As is true of all humans at all ages, emotional memories are particularly strong in AD.

Axiom XI: All human beings have the capacity to think. As with other basic human capacities, this one is sometimes not recognized in the AD patient—with deleterious consequences. For example, caregivers may sometimes speak unflatteringly about the late stage 6 and early stage 7 AD patient, thinking that, because the patient cannot articulate, he or she does not understand. The patient may become agitated in response to the caregiver's unempathetic comments. Unfortunately, the caregiver, not recognizing the patient's comprehension, may think the agitation is sporadic and arbitrary, rather than a response to the crude and critical remarks.

Axiom XII: All human beings seek to influence their environment. This basic human need and desire is also frequently underestimated in the stage 7 AD patient. For pret a stage 7 AD patient's babbling, the patient seeks to make their desire known and many become agitated, or violent, if not "listened to."

Axiom XIII: All human beings have a sense of "taste," i.e., likes and dislikes. Just as infants will throw away a toy they do not like, an AD patient has preferences that are expressed and can be interpreted at any stage. These preferences are sometimes not recognized. For example, a case manager recommended "any ID bracelet" for an early stage 6 AD patient because "she won't notice." In actuality, this patient would have been highly insulted by an unattractive plastic bracelet and wished to maintain a sense of style and beauty.

Care postulates

The postulates are based on the retrogenesis observations and the DA model of the stages of AD, reviewed in the preceding sections. The validity of the postulates is subject to scientific investigation. A summary of some of the major postulates follows.

Postulate I: The magnitude of care and supervision required by an AD patient, at a DA, is mirrored by the amount of care and supervision required by a child or infant at the corresponding DA. For example, an AD patient at GDS and FAST stage 7, corresponding to an infancy DA, requires approximately the same amount of care and supervision as an infant.[29]

Postulate II: The kinds of activities enjoyed by an AD patient, at a particular DA, are mirrored by the kinds of activities enjoyed by children at a corresponding DA. For example, just as child of age two to five years may enjoy working on puzzles, drawing with crayons, or assisting with simple household chores, similar activities are appropriate for the GDS and FAST stage 6 AD patient at a corresponding DA.

Corollaries of postulate II include the following:

- The kinds of activities that children find frightening or upsetting at a DA are mirrored by the kinds of activities AD patients find upsetting at a corresponding DA;
- The kinds of activities that a child considers "childish" or "babylike" at a particular DA, are mirrored by the kinds of activities an AD patient may find humiliating; and
- The kinds of activities that promote healthy and optimal motor development in children are similarly the kinds of activities which minimize motor degeneration in AD.

form in an area of residual expertise is dependent on the patient's DA. If a child at the particular DA can master the task, an AD patient at the corresponding DA potentially can retain the residual capacity. Variability in AD patients' loss of capacity is mirrored by a corresponding variability in children's ability to master the task. Therefore, expectations must be in accord with the DA of the AD patient. A corollary of this postulate is that as an AD patient approaches loss of capacity, they develop anticipatory anxieties. For example, AD patients commonly develop anxieties regarding toileting in FAST stage 6c, prior to loss of urinary continence in FAST stage 6d. Similarly, some patients develop anxieties about completing their income tax in GDS and FAST stage 4.

Postulate IV: Previous experiences may determine the kinds of activities enjoyed by an AD patient. For example, one GDS stage 6, FAST stage 6d AD patient was very anxious about having her front yard clean. Naturally, an urban patient might not be interested in cleaning a yard.

Postulate V: The emotional level of the AD patient is dependent on the DA. For example, just as a two to three year-old child may become "cranky" at various points in the day, a stage 6d AD patient at a corresponding DA may develop "mood swings."

Postulates VI: Life experiences appropriate to the DA become most relevant for AD patients at any particular stage. For example, a man's only interest may have been his work. However, at stage 5 (DA of five to seven years), much of the interest in his previous job (*e.g.*, business, medicine, etc.) is lost. At this point, DA-appropriate activities can be introduced.

Postulate VII: Socialization of the AD patient is dependent on the DA. For example, just as an infant of a year old or less does not yet relate socially with other infants, a GDS and FAST stage 7 AD patient does not relate or socialize with other stage 7 patients.

Postulate VIII: Diversity in children's and infants' activities and interests is mirrored in diversity in AD patient's interests and activities at a corresponding DA. A corollary of this is that just as all normal, healthy, children at a given age clearly can be shown to have much in common, despite acknowledged diversity, all "uncomplicated" AD patients at a given stage have much in common, despite acknowledged diversity. For example, all normal, healthy, one-year-old children have much in common with each other in comparison with normal, healthy, 12-year-old children. Conversely, all GDS stage 7, FAST stage 7a, uncomplicated AD patients have much in common, as compared to all uncomplicated stage 4 AD patients.

at a DA are mirrored by the emotional changes observed in children at a corresponding DA. This is similar to postulate V, but concerns specifics. For example, delusions occur in AD patients that are very similar to childhood fantasies at the corresponding DAs.[27-29]

Postulate X: Care settings appropriate to AD patients at a DA are mirrored by care settings appropriate to children at the corresponding DA.[29] A corollary of this postulate is that just as institutions would be considered an inappropriate and undesirable care setting for infants and toddlers, institutions are inappropriate settings for the care of GDS and FAST stage 7 and stage 6 AD patients. Therefore, resources currently devoted to nursing home care probably should be shifted to care in community residences.

The analogy of nurseries and schools for children to day-care centers for AD patients also applies in this regard.

Postulate XI: Vulnerability (emotional, physical, and cognitive) of the AD patient at a DA is mirrored by the vulnerability of children at the corresponding DA. For example, just as an infant is vulnerable to social deprivation, poor care, and physical insult, a stage 7 AD patient is vulnerable to social deprivation, poor care, and physical insult. The result of these social, emotional, and physical injuries is excess disability.

Postulate XII: The need of an AD patient for physical movement is mirrored by the corresponding DA. A young child requires more than simply walks or running back and forth for optimal physical growth and attainment. Motor development in children is also dependent on the child dressing, developing eating skills, ball playing, and other skills. The same kinds of skills are required by the AD patient to prevent precipitous physical decline.

Postulate XIII: Just as one judges development in an infant or child by what the infant or child can do and has achieved, not by what the infant or child cannot do, the AD patient at any particular DA should be assessed in terms of his or her residual skills and accomplishments, what they have learned and relearned, not by what they cannot do.

Postulate XIV: The developmental analogy is sufficiently strong to trigger DA-appropriate childhood memories, beliefs, and anxieties in the AD patient. For example, most FAST stage 6e AD patients will state that their parents are alive. These DA-appropriate memories are the basis of the statement, incorporated in the Blessed *et al.* dementia scale, that AD patients tend to dwell in the past.[69]

Postulate XV: The language changes of the AD patient are mirrored by the DA. For example, when

speech abilities break down in the AD patient at FAST stage 6e, patients commonly develop "verbigeration" and neologisms, which are very similar to the babbling of infants as they acquire speech at an equivalent DA.

Care caveats

Caveats which modify the retrogenic-DA model of AD make the care and management of the AD patient a complex art as well as a science. Some of the major caveats are enumerated below.

Caveat I: Development in infants and children is accompanied by increasing expectations, whereas AD at all stages is accompanied by progressively diminished expectations. These contrasting phenomena are accompanied by widely divergent social consequences. For example, the societal tendency is to praise children and to become frustrated with AD patients. However, growth, within the context of an individual's capacity for growth, is dependent on praise for one's accomplishments.

Caveat II: AD patients experience developmentally analogous brain changes; however, they do not undergo developmentally analogous physical changes. Therefore, AD patients are physically larger and more formidably appearing than children. Furthermore, until stage 7, AD patients have the physical habitus of a normal adult. These physical features produce special consequences for AD patients in comparison with children. For example, the AD patient's normal appearance conveys a level of sagacity and competence, which is not assumed to be present in children at the same DA.

Also, because of the absence of a physical retrogenesis, the physical capacities of the AD patient may sometimes exceed those of DA-comparable children and infants. For example, a very well cared for GDS stage 7, FAST stage 7b patient who receives retraining can be relatively dexterous as compared to a one-year-old. For example, one GDS 7, FAST 7b patient was able to lace, button, and slip on clothing.

Another consequence of the AD patients' size and strength in comparison with their DA peers is that a grasp reflex in a stage 7 AD patient can be much stronger and more difficult to release then an infant's grasp reflex, with consequences for the management of the AD patient.[76]

Caveat III: AD patients can, to some extent, draw upon previously mastered skills, whereas infants and children may not have access to these skills. Consequently, AD patients may be relatively skilled and "precocious" in comparison with their chronologically younger DA peers. For example, even in late stage 7, long after serviceable speech has been lost, AD patients may occasionally (*e.g.*, during their sleep, or in response to startle or pain) utter seemingly forgotten words. Infants do not have access to such words.

Caveat IV: AD patients can, to some extent, draw upon previously mastered knowledge, whereas infants and children may not have access to this knowledge. For example, a GDS and FAST 7d AD patient who always had an immaculate household uttered "aagh!" when a caregiver dropped shoes in the middle of the floor. This same 7d AD patient would "whack" a caregiver who put her elbows on the table.

Caveat V: AD patients are older than their DA peers, and old age predisposes to various physical disabilities that influence the life and experience of an AD patient. For example, cataracts predispose AD patients to visual hallucinations.

Caveat VI: AD patients appear to be more prone to rigidity than their DA peers. The causes probably include the AD patients' brain disease in the absence of physical involution and the relative immobility of AD patients. The rigidity can greatly increase disability in the AD patient, ultimately resulting in contractures.

Caveat VII: AD patients can potentially concentrate on a task longer than infants or children at a corresponding DA. Conversely, infants and children are more distractible and impatient than AD patients. For example, one GDS 7, FAST 7c AD patient is known to stare at a newspaper for perhaps an hour. An 11-month-old infant will look at a book for a few minutes.

Caveat VIII: AD patients appear to be less fascinated by the world and less inquisitive than infants and children at a corresponding DA. For example, a two-year-old child may continuously ask questions, such as "What is this?" whereas an AD patient at GDS 6, FAST stage 6e is not inquisitive in this manner.

Care science

Therefore, a care science in AD can be firmly grounded in universal human, retrogenic, and AD-specific principles. The ingredients for the quality care recipe can now be described in considerable detail. These principles can potentially impact positively on the quality of life and excess disability of AD patients at this juncture. Potentially, much of the suffering and distress associated with AD can be relieved.

Pharmacologic treatment of the biomolecular retrogenic process

The nascent understanding of the role of mitogenic factors in the etiopathogenesis of AD has suggested new avenues for fundamental treatment investigations. In many ways, the mitogenic response of biomolecular retrogenesis to AD-associated stressors and toxins is similar to

the mitogenic response to stressors and toxins in non-nervous-system tissues.[71-73] In other organ systems and tissues, the stressors and toxins producing a mitogenic response are termed *carcinogens* and the mitogenic response is termed a *neoplastic response*. In the adult brain, despite the occasional occurrence of neurogenesis, an abortive neurogenesis or abortive mitosis is associated with neurofibrillary changes and, perhaps, apoptosis. Consequently, antineoplastic agents that suppress mitosis may have relevance for the treatment of AD.

Conclusion

In summary, retrogenesis appears to represent a new mechanism of disease with distinct biomolecular, pathologic, physiologic, and clinical manifestations. Distinct management and treatment principles and avenues for pharmacologic research follow from these retrogenic mechanisms and their manifestations. AD is the paradigmatic retrogenic disorder, but the process is applicable to a variable extent to many other dementing conditions.

Authors' note

The methodology described herein of a science of management, care, and treatment of Alzheimer's disease and related dementias is the subject of a pending patent application.

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Calendar

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ORIGINAL CONTRIBUTION

Effects of Rofecoxib or Naproxen vs Placebo on Alzheimer Disease Progression

A Randomized Controlled Trial

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Context Laboratory evidence that inflammatory mechanisms contribute to neuronal injury in Alzheimer disease (AD), along with epidemiological evidence, suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may favorably influence the course of the disease.

Objective To determine whether treatment with a selective cyclooxygenase (COX) -2 inhibitor (rofecoxib) or a traditional nonselective NSAID (naproxen) slows cognitive decline in patients with mild-to-moderate AD.

Design Multicenter, randomized, double-blind, placebo-controlled, parallel group trial, with 1-year exposure to study medications.

Setting Forty ambulatory treatment centers affiliated with the Alzheimer's Disease Cooperative Study consortium.

Participants Participants with mild-to-moderate AD (Mini-Mental State Examination score of 13-26) were recruited from December 1999 to November 2000 using clinic populations, referrals from community physicians, and local advertising. Stable use of cholinesterase inhibitors, estrogen, low-dose aspirin, and vitamin E was allowed. Participants with inflammatory diseases that might respond to the study medications were excluded. Of 474 participants screened, 351 were enrolled.

Interventions Once-daily rofecoxib, 25 mg, or twice-daily naproxen sodium, 220 mg, or placebo.

Main Outcome Measures The primary outcome measure was the 1-year change in the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) subscale score. Secondary outcome measures included the Clinical Dementia Rating scale sum-of-boxes, the Neuropsychiatric Inventory, the Quality of Life-AD, and the time to attainment of significant end points (4-point decline from baseline ADAS-Cog score, 1-step worsening on the global Clinical Dementia Rating scale, 15-point decline on the ADCS activities of daily living inventory, institutionalization, or death).

Results The 1-year mean (SD) change in ADAS-Cog scores in participants treated with naproxen (5.8 [8.0]) or rofecoxib (7.6 [7.7]) was not significantly different from the change in participants treated with placebo (5.7 [8.2]). Results of secondary analyses showed no consistent benefit of either treatment. Fatigue, dizziness, and hypertension were more commonly reported in the active drug groups, and more serious adverse events were found in the active treatment group than in the placebo group.

Conclusion The results of this study indicate that rofecoxib or low-dose naproxen does not slow cognitive decline in patients with mild-to-moderate AD.

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ALZHEIMER DISEASE (AD) IS among the most important health problems of elderly persons, affecting more than 4 million people in the United States. In the last decade, cholinesterase inhibitors have been widely used to alleviate symptoms of cognitive dysfunction in AD. The use of anti-inflammatory drugs is among the strategies under active investigation for the development of effective disease-modifying treatment for AD. This approach is supported by a wealth of laboratory evidence that inflammatory mechanisms contribute to neuronal damage in AD.[1] Furthermore, many epidemiological studies suggest that anti-inflammatory drugs have a protective effect, reducing the incidence of AD.[2]

Results of small pilot clinical trials of nonsteroidal anti-inflammatory drug

For editorial comment see p 2865.

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(NSAID) efficacy in the treatment of AD have been encouraging. One report indicated a stabilizing effect of indomethacin treatment for 6 months,[3] while a follow-up study showed a trend toward benefit with diclofenac treatment for 25 weeks.[4] Neither study showed conclusive results, and the patients with AD showed poor tolerability of both drugs. Larger studies with better tolerated treatment regimens, such as low-dose prednisone for 1 year[5] and hydroxychloroquine for 18 months,[6] failed to demonstrate benefit in the treatment of AD.

Recent studies have provided strong support for the testing of efficacy of NSAIDs in the prevention of AD. A large epidemiologic study using computerized medical records to accurately indicate drug use corroborates earlier work, with evidence that use of NSAIDs sharply reduces AD risk.[7] In transgenic mice with AD-type amyloid deposition, the NSAID ibuprofen reduced brain inflammation and levels of soluble and insoluble amyloid peptide, and improved behavior.[8,9]

In this trial, we tested the hypothesis that NSAID treatment would slow the rate of cognitive decline in participants with mild-to-moderate AD. Selection of treatment regimens was based on consideration of the appropriate target in AD brain, as well as medication tolerability. Results of studies in cell culture systems,[10,11] rodents,[12,13] and human brain[10,14] indicate that neuronal upregulation of cyclooxygenase (COX) -2 may contribute to neurodegeneration in AD. However, the epidemiological data support the efficacy of long-term use of low doses of nonselective NSAIDs that inhibit COX-1 and COX-2,[7] and microglial COX-1 may be an important target.[15] Long-term treatment with full doses of nonselective NSAIDs has been associated with a substantial risk of serious gastrointestinal tract toxicity. Therefore, we used a standard dose of the selective COX-2 inhibitor rofecoxib and a low-dose of the nonselective NSAID naproxen. We chose a treatment period of 1 year based on evidence from a pilot study of NSAID efficacy with short-term treatment[3] and the concern about the risk of long-term exposure in individuals with AD.

METHODS

Study Design

The study used a randomized, double-blind, 3-group parallel design to compare rofecoxib or naproxen with placebo. The treatment period was 12 months, followed by a 2-month washout. Forty ambulatory treatment centers affiliated with the Alzheimer's Disease Cooperative Study (ADCS) consortium participated in this trial after obtaining approval from their local institutional review boards. Written informed consent was obtained from participants and/or legally authorized representatives, according to local guidelines.

Individuals with probable AD[16] recruited from December 1999 to November 2000 using clinic populations, referrals from community physicians, and local advertising were eligible if they did not have comorbid conditions that increased the risk of adverse events associated with NSAID treatment (hypersensitivity to aspirin or NSAIDs, active peptic ulcer disease within 5 years, renal insufficiency [serum creatinine level >1.5 mg/dL or >132.6 μmol/L], clinically significant liver disease, poorly controlled hypertension, congestive heart failure, or bleeding disorder). Individuals were excluded if they had comorbid conditions that might respond to NSAIDs (eg, inflammatory arthritis). Individuals also were excluded if within the prior 2 months they had regularly used anti-inflammatory medications (aspirin at a daily dose ≤325 mg was allowed), neuroleptics, antidepressants, sedatives, anti-Parkinsonian medications, or any investigational treatment for AD. Inclusion criteria included age older than 50 years and Mini-Mental State Examination (MMSE)[17] score within the range of 13 to 26. Stable use of cholinesterase inhibitors was allowed.

Rofecoxib tablets, 25 mg, were over-encapsulated to allow preparation of an identical placebo capsule. Naproxen sodium tablets, 220 mg, and identical placebo tablets were supplied by Bayer Consumer, Inc (Morristown, NJ). Each participant received 2 bottles of study medication with coded labels at baseline and at the 3-, 6-, and 9-month visits: 1 bottle containing rofecoxib or identical placebo capsules, to be taken once daily; and 1 bottle of naproxen or identical placebo capsules, to be taken twice daily.

The randomization process used a permuted block design with block size of 3 stratified by site. The randomization sequence was generated by the ADCS data center. Scratch-off codebreakers were used so that instances of unblinding would be documented; all codebreakers were collected at the end of the trial. Adequacy of masking was assessed by questionnaires completed by participants, caregivers, psychometrists, and site investigators.

Safety assessments, including vital signs, physical examination, urinalysis, and hematology and chemistry blood tests, were performed at each visit. Cognitive and behavioral assessments were performed at baseline and at months 1, 3, 6, 9, 12, and 14.

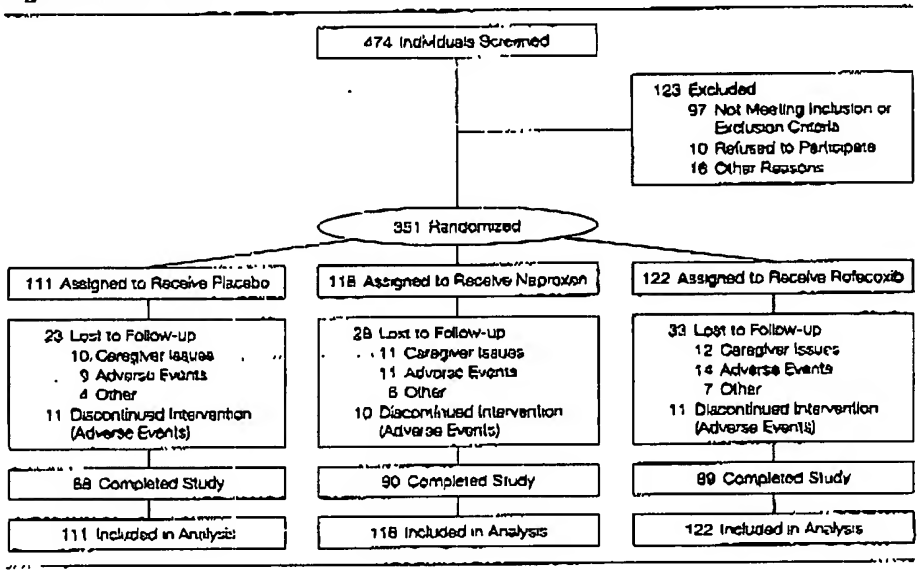
Outcome Measures

The primary outcome measure for this trial was the 1-year change score on the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) subscale,[18] an instrument that evaluates memory, attention, reasoning, language, orientation, and praxis. We considered a significant benefit in the active group to be a 50% reduction in cognitive decline as indicated by change in ADAS-Cog score compared with the placebo group. Data from a small pilot study[3] have supported the hypothesis that an effect of this magnitude might be seen, and we considered that a smaller effect might not justify the risk of long-term NSAID therapy in the AD participants. Using longitudinal ADAS-Cog data from an earlier multicenter trial,[5] we estimated that 100 participants were required in each treatment group (naproxen, rofecoxib, and placebo) for a power of 0.8. An overall drop-out rate of 20% was anticipated. Since we ex-

pected more drop-outs from adverse drug effects in the active drug groups, fewer participants were randomly assigned to the placebo group (participants were randomly assigned using a ratio of 1.2 [naproxen]:1.2 [rofecoxib]:1.1 [placebo]).

Secondary outcome measures included the Clinical Dementia Rating sum-of-boxes (CDR-SOB),[19] Alzheimer's Disease Cooperative Study activities of daily living (ADCS-ADL) scale,[20] the Neuropsychiatric Inventory (NPI),[21] the Quality of Life-AD (QOL-AD),[22] and the time to attainment of significant end points (4-point decline from baseline ADAS-Cog score, 1-step worsening on the global CDR scale, 15-point decline on the ADCS-ADL, institutionalization, or death).

Figure. Patient Flow



Statistical Analysis

The primary analysis was a comparison of the change in ADAS-Cog score between the naproxen and rofecoxib groups and the placebo group using analysis of covariance (ANCOVA), with the baseline ADAS-Cog score as a covariate. The statistical plan included assessment of the treatment groups for significant imbalance in age, sex, or apolipoprotein E genotype that might influence outcome; if an imbalance was present ($P<.15$) and the factor influenced ADAS-Cog change scores ($P<.10$), it would be included in the ANCOVA model.

The primary analysis was conducted on an intent-to-treat basis (ie, including all randomized participants). Because AD is a disease of progressive cognitive deterioration, the protocol specified an alternative imputation scheme rather than last-observation-carried-forward (LOCF) analysis. (LOCF analysis would overestimate a treatment effect if an excess of drop-outs occurred in the active drug group due to adverse effects.) To impute a participant's missing score at week 52, an estimate of change in ADAS-Cog score during the unobserved period based on all individuals with complete data from the participant's treatment group was applied to the participant's last observed score. A linear rate of progression was not assumed. We also conducted secondary analyses of change in ADAS-Cog scores using the LOCF imputation, and an analysis of completers only (ie, those who completed the week 52 visit). In addition, we conducted a longitudinal regression analysis using the method of generalized estimating equations.[23] For this analysis, a pair-wise comparison of the naproxen group vs the placebo group and the rofecoxib group vs the placebo group, the outcome was the ADAS-Cog score clustered by the baseline, 3-, 6-, 9-, and 12-month visits.

A planned secondary analysis of time to reach clinically significant end points was performed using a Cox proportional hazards model. Intent-to-treat analysis of secondary measures were conducted using both the slope imputation strategy described above and LOCF for missing week 52 values. No interim analysis was performed. Statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

The flow of participants through the study protocol is shown in FIGURE 1. From a total of 474 participants screened, 351 met the study criteria and were randomly assigned to 1 of the 3 treatment groups (rofecoxib, naproxen, or placebo). Considering the likelihood that more participants in the active groups would drop out due to adverse effects, more participants were randomly assigned to rofecoxib (n=122) and naproxen (n=118) than to the placebo group (n=111).

The primary outcome measure (change in ADAS-Cog score at week 52) was obtained for study completers: 90 (76%) participants in the naproxen group, 89 (73%) in the rofecoxib group, and 88 (79%) in the placebo group. The predominant reasons for early study discontinuation were caregiver issues (rofecoxib, n=12; naproxen, n=11; and placebo, n=10) and adverse events (rofecoxib, n=14; naproxen, n=11; and placebo, n=9).

The demographic and clinical characteristics of the treatment groups at baseline are shown in TABLE 1. No significant differences were found between the groups on any of the demographic or baseline characteristics. Eighty-seven participants (25%) were using low-dose aspirin during the trial: 33 (27%) in the rofecoxib group, 30 (25%) in the naproxen group, and 24 (22%) in the placebo group. Aspirin use

Table 1. Participant Demographics and Assessment Scores at Baseline

	Placebo (n = 111)	Naproxen (n = 118)	P Value*	Rofecoxib (n = 122)	P Value*
Age, mean (SD), y	73.8 (8.0)	74.1 (7.6)	.78	73.7 (7.2)	.96
Sex, female, %	55.9	48.3	.31	54.9	.99
Education, mean (SD), y	14.3 (3.3)	13.8 (3.2)	.37	13.8 (3.2)	.24
Duration of disease, mean (SD), y	4.2 (3.3)	4.1 (2.3)	.92	4.1 (2.3)	.89
Users of cholinesterase inhibitors at baseline, No. (%)	74 (67)	78 (66)	.99	88 (70)	.57
Participants starting cholinesterase inhibitors during the study, No. (%)	6 (5)	10 (8)	.44	8 (7)	.79
Users of low-dose aspirin, No. (%)	24 (22)	30 (25)	.54	33 (27)	.36
Apolipoprotein E, No. (%) with ≥1 E4 allele	67.6	70.4	.68	68.1	.95
MMSE score, mean (SD)†	20.8 (3.6)	20.7 (3.6)	.81	21.2 (3.8)	.87
ADAS-Cog score, mean (SD)†	24.2 (9.4)	24.4 (10.2)	.92	23.4 (9.4)	.45
CDR sum-of-boxes score, mean (SD)†	5.5 (2.5)	6.0 (2.9)	.28	5.6 (2.5)	.82

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale-Cognitive subscale; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

*P values for comparison with placebo, using the Wilcoxon test for continuous variables and the Fisher exact test for frequencies.

†The range of scores for MMSE is 0 to 30 points; for ADAS-Cog, 0 to 70 points, and CDR sum-of-boxes, 0 to 18 points.

did not show a significant effect on ADAS-Cog scores for all groups or for the individual treatment groups.

Baseline characteristics were compared between participants who discontinued early and those who completed the study. In the naproxen group, participants who discontinued early had lower mean (SD) MMSE scores (19.6 [3.3] vs 21.0 [3.6]; P=.04; using Wilcoxon rank sum test) and higher mean (SD) CDR-SOB scores (7.2 [3.4] vs 5.7 [2.7]; P=.03). No significant differences were found between the rofecoxib and placebo groups.

A total of 238 (68%) participants were taking cholinesterase inhibitors at the time of enrollment. Twenty-four participants (rofecoxib group, n=8; naproxen group, n=10; and placebo group, n=6) started treatment with cholinesterase inhibitors prior to the month 12 visit. These participants were included in the primary intent-to-treat analyses. In a secondary analysis of the main outcome measure excluding these 24 subjects, the results were similar (data not shown).

Analysis of Outcomes

Primary Outcome Measure. The effect of treatment on the primary and secondary measures in the intent-to-treat analysis is shown in TABLE 2. None of the planned covariates (age, sex, and apolipoprotein E genotype) was included in the analysis, because there was neither imbalance nor association with the outcome.

Neither active treatment had a beneficial effect on the primary measure, the change in mean ADAS-Cog scores; the group treated with rofecoxib showed a trend toward greater cognitive decline compared with the other groups. For the comparison of naproxen with placebo, the SE of the difference between change scores was 1.07 (95% confidence interval for the difference in the change scores, −0.1 +/− 2.14); therefore, it is highly unlikely that naproxen treatment reduces the 1-year decline in ADAS-Cog score by more than 2.04/5.7, or 36%. For the comparison of rofecoxib with placebo, the SE of the difference between change scores was 1.03; a similar calculation indicates it is highly unlikely that rofecoxib reduces the decline in ADAS-Cog score by more than 15%.

When LOCF imputation of the change in ADAS-Cog score was substituted for the primary imputation scheme, the result was similar to the primary analysis (mean [SD] ADAS-Cog change in score in the placebo group, 4.9 [8.2]; rofecoxib group, 5.9 [7.7], P=.52; and naproxen group, 5.0 [7.9], P=.94). Analysis of participants taking study medication who completed the 52-week visit yielded similar results, with no significant difference in rate of decline for the mean (SD) ADAS-Cog score (placebo, 5.3 [8.5], n=79; rofecoxib, 6.8 [7.7], n=78, P=.47; naproxen, 5.3 [7.9], n=80, P=.9). Regression analysis using the generalized estimating equations method demonstrated no effect of rofecoxib (P=.77) or naproxen (P=.64) on longitudinal ADAS-Cog scores.

Secondary Outcome Measures. The intent-to-treat analysis using the primary imputation scheme for missing values revealed no significant difference in decline for the CDR-SOB scores across all the groups (Table 2). Other analyses, using LOCF imputation or assessing completers only, showed similar results (data not shown). The ADCS-ADL scores showed a trend toward a beneficial effect with use of rofecoxib. However, none of the secondary analyses were adjusted for multiple comparisons because this was not specified in the original protocol. In the slope imputation analysis, use of rofecoxib reduced the decline in ADCS-ADL score by 22% (unadjusted P=.09); in the LOCF analysis, use of rofecoxib reduced the decline in ADCS-ADL score by 33% (unadjusted P=.04). In an analysis of study completers only, rofecoxib reduced the decline in ADCS-ADL score by 27% (unadjusted P=.09). Treatment with rofecoxib or naproxen had no effect on the NPI or QOL-AD scores.

The planned survival analysis considered the time interval from the baseline visit to the first among 5 possible end points: death, institutionalization, increase in global CDR score, 15-point decline on the ADCS-ADL scale, or 4-point decline on the ADAS-Cog scale. A total of 242 subjects (69%) reached at least 1 end point (placebo group, n=78 [70%]; naproxen group, n=83 [70%]; and rofecoxib, n=81 [66%]). Rofecoxib (P=.63) or naproxen (P=.50) vs placebo did not differ in time to first end point. When time to individual end

Table 2. One-Year Change in Assessment Scores in the Intent-to-Treat Analysis*

	Placebo (n = 111), Mean (SD)			Naproxen (n = 118), Mean (SD)			P	Rofecoxib (n = 122), Mean (SD)			P
	Baseline	1 Year	Change	Baseline	1 Year	Change	Value†	Baseline	1 Year	Change	Value†
ADAS-Cog	24.2 (9.6)	29.9 (13.7)	−5.7 (8.2)	24.4 (10.2)	30.2 (13.9)	−5.8 (8.0)	.96	23.4 (9.4)	31.0 (13.2)	−7.6 (7.7)	.09‡
CDR-SOB	5.5 (2.5)	7.7 (3.9)	−2.2 (2.3)	6.0 (2.9)	8.3 (4.0)	−2.3 (2.3)	.89	5.6 (2.5)	7.8 (3.5)	−2.2 (2.4)	.89
ADCS-ADL	62.8 (11.4)	51.3 (16.3)	−11.5 (11.2)	60.0 (13.1)	51.3 (16.3)	−8.7 (10.5)	.14	62.2 (11.4)	53.9 (14.4)	−8.3 (9.7)	.08
NPI	8.7 (10.6)	12.2 (12.8)	−3.4 (11.9)	9.4 (9.6)	13.1 (14.4)	−3.7 (12.5)	.76	9.2 (9.6)	13.1 (14.2)	−3.8 (10.9)	.76
QOL-AD	36.7 (5.8)	34.3 (6.0)	−2.4 (5.1)	37.0 (5.9)	34.5 (6.2)	−2.6 (5.5)	.93	36.7 (5.9)	33.8 (6.2)	−2.9 (5.6)	.85

Abbreviations: ADAS-Cog, Alzheimer Disease Assessment Scale-Cognitive subscale; ADCS-ADL, Alzheimer Disease Cooperative Study-Activities of Daily Living; CDR-SOB, Clinical Dementia Rating sum-of-boxes; NPI, Neuropsychiatric Inventory; QOL-AD, Quality of Life, Alzheimer Disease.

*For each scale, negative change scores indicate deterioration and positive change scores represent improvement. The range of points for ADAS-Cog is 0 to 70; CDR-SOB is 0 to 18; ADCS-ADL is 0 to 78; NPI is 0 to 144; and QOL-AD is 13 to 52.

†*P* values for comparison with placebo.

‡Holm adjustment applied to the *P* value for the ADAS-Cog. The purpose of the Holm adjustment is to account for planned multiple comparisons in the primary end point analysis, thus ensuring an overall type 1 error ≤.05: if either comparison yields $P \leq .05$, the smaller *P* value is doubled. The unadjusted *P* value was .044 for the rofecoxib-placebo comparison for ADAS-Cog.

points was examined, the only significant difference was between the rofecoxib and placebo groups for time to institutionalization, favoring the rofecoxib group ($P = .03$) (data not shown). However, this analysis was based on a small number of events (7 in the placebo group and 1 in the rofecoxib group), and the *P* value was not adjusted for multiple comparisons.

Table 3. Adverse Events Reported More Frequently by Participants in the Active Treatment Groups

	Placebo, No. (%)	Naproxen, No. (%)	*P* Value*	Rofecoxib, No. (%)	*P* Value†
Fatigue	7 (6)	17 (14)	.08	18 (15)	.05
Dizziness	5 (5)	14 (12)	.08	14 (11)	.08
Dry mouth	1 (1)	6 (5)	.06	1 (1)	>.99
Hypertension	0	6 (5)	.03	9 (7)	.004

*For comparison of naproxen vs placebo

†For comparison of rofecoxib vs placebo.

Adverse Events

Treatment emergent adverse events were grouped into categories for analysis. Naproxen and rofecoxib groups had more frequent adverse event reports ($P < .10$) (TABLE 3). Dizziness and fatigue were more common in the active drug groups than in the placebo group, and dry mouth was more common in the naproxen group than the placebo group. New cases of hypertension were reported as adverse events in the active drug groups, but none were reported in the placebo group (naproxen [n = 6] vs placebo [n = 0], $P = .03$ and rofecoxib [n = 9] vs placebo, $P = .004$).

In addition to adverse events reported on case report forms, study participants were asked about a list of symptoms that might arise with NSAID treatment. When the proportion of each treatment group reporting new symptoms (not present at baseline) was compared, the difference was significant compared with placebo for dry mouth (10% for naproxen vs 2% for placebo; $P = .01$) and muscle pain (13% for rofecoxib vs 4% for placebo; $P = .03$). The percentage of participants with new reports of any gastrointestinal tract symptom did not differ among the treatment groups (37% for naproxen, 31% for rofecoxib, and 30% for placebo).

Despite the cases of hypertension noted above, mean blood pressure did not differ significantly by treatment group. The effects of treatment group on mean (SD) change were minimal for hematocrit (placebo [n = 87]: −0.3% [2.2]; naproxen [n = 88]: −1.0% [2.2] vs placebo, $P = .01$; and rofecoxib [n = 87]: −1.2% [2.2] vs placebo; $P = .05$) and for serum creatinine (0.02 [0.13] mg/dL or 1.8 [11.5] µmol/L, n = 88; naproxen [n = 87]: 0.02 [0.13] mg/dL or 1.8 [11.5] µmol/L, vs placebo, $P = .90$; and rofecoxib [n = 84]: 0.08 [0.16] mg/dL or 7.1 [14.1] µmol/L vs placebo, $P = .01$).

The total number of serious adverse events in each treatment group, along with number of events within specific categories, did not differ significantly (TABLE 4).

Success of Blinding

The randomization code was broken in 1 instance, based on clinical need for the management of an acute medical problem. Study personnel involved in administering assessment tools were shielded from group assignment data in this instance.

The results of questionnaires administered at the month 12 visit indicated that the percentage of participants who believed they were taking active study medication also did not differ significantly across the treatment groups (rofecoxib group, 70%; naproxen group, 74%; and placebo group, 73%; $P = .82$, Fisher exact test), indicating that blinding was adequately maintained.

At the 12-month visit, the percentage of informants who believed that participants were taking active study medication also did not differ across the participants' treatment group (52% for rofecoxib group, 51% for naproxen group, and 59% for placebo group; $P = .10$, Fisher exact test). The differences also were not significant for study coordinators (54% for rofecoxib group, 50% for naproxen group, and 43% for placebo group; $P = .52$, Fisher exact test) and study physicians (56% for rofecoxib group, 40% for naproxen group,

Table 4. Number of Serious Adverse Events

	Placebo	Naproxen	Rofecoxib
Total serious events	15	25	26
Deaths	1	1	2
Gastrointestinal tract event*	1	2	4
Stroke/transient ischemic attack	1	3	3
Subdural hematoma	0	2	1
Myocardial infarction	1	0	3

*Serious gastrointestinal tract events included 6 cases of gastrointestinal tract bleeding and 1 case of perforated small intestine (the latter occurred in the naproxen group).

and 40% for placebo group; $P = .19$, Fisher exact test).

COMMENT

This is the first large-scale trial, to our knowledge, to determine the efficacy of both nonselective and COX-2 selective NSAIDs in the treatment of AD. The result of the primary intent-to-treat analysis of this trial showed that neither naproxen nor rofecoxib slowed the rate of cognitive decline in comparison with placebo in participants with mild-to-moderate AD. Similar results were obtained when an LOCF analysis was substituted for the primary slope method of imputing missing 12-month data and when the data were analyzed using the generalized estimating equations method. The results of an analysis of study completers (those who were able to complete the trial while still taking study medication) also revealed no beneficial treatment effect of the active study drugs in comparison with placebo. Instead, the rofecoxib group showed a trend toward greater cognitive decline compared with placebo.

In the naproxen group, baseline MMSE and CDR-SOB scores differed between individuals who discontinued study participation early and those who completed the study. This difference raises the possibility that imputation of the data missing from noncompleters may have influenced the outcome of the primary analysis. However, the nonsignificant finding of the primary analysis is in agreement with the nonsignificant findings of the LOCF analysis, the completers analysis, the generalized estimating equations regression analysis, and the clinical end points survival analysis, which strongly support its validity.

Secondary analyses of the effect of treatment on a global measure of cognitive decline, behavior, ADL, and quality of life showed no consistent advantage of either treatment over placebo. Rofecoxib delayed the time to institutionalization, but this result was based on a small number of end points. Adjustment for multiple comparisons would have made this comparison nonsignificant.

In some analyses, there was a trend toward smaller decline in ADL with active treatment, particularly with rofecoxib. The trend toward greater cognitive decline with rofecoxib treatment suggests that the trend toward protection against decline in ADL may be related to an analgesic effect rather than an effect on AD.

Both active treatments were reasonably well tolerated, although participants who dropped out due to adverse events were more commonly from the active drug groups than from the placebo group. Surprisingly, the gastrointestinal tract symptoms were similar in the 3 groups. The small number of serious gastrointestinal tract events (primarily bleeding) in the active drug groups was consistent with expected risks. The occurrence of adverse events likely was reduced by excluding individuals at high risk of NSAID toxicity.

Two important issues must be raised when interpreting the lack of active treatment effect. The first issue concerns selection of drug, dose, and duration of treatment. Naproxen was selected because the epidemiological evidence supports the efficacy of nonselective COX inhibitors, and naproxen has a long half-life (allowing for twice-daily dosing) and is relatively well tolerated. The naproxen dose was low because of concern that full-dose therapy with a nonselective COX inhibitor would be associated with more serious adverse events and a high dropout rate compared with placebo. The nonsignificant results with naproxen could be explained by an insufficient dose; alternatively, other drugs in this same class, such as ibuprofen, may have greater activity in AD mediated by an effect on processing of the amyloid precursor protein.[24] Rofecoxib, 1 of 2 available selective COX-2 inhibitors at the time this study was initiated, was administered at a standard, full anti-inflammatory dose. It is possible that a higher dose is necessary to influence neuronal survival; a high dose of celecoxib, above the standard anti-inflammatory dose, is required to influence neoplastic transformation in the gastrointestinal tract.[25] It is also possible that a period of exposure to anti-inflammatory treatment greater than the 1 year of treatment in this trial is necessary to slow the disease process. Some epidemiological studies of AD prevention suggest that at least 2 years of exposure is necessary to optimally reduce risk of AD.[26,27]

The second issue concerns the selection of participants. The most compelling epidemiological evidence suggests that long-term exposure to NSAIDs reduces risk of subsequent AD; on the other hand, some studies suggest a stabilizing effect of NSAID therapy in patients with clinically evident disease,[3,28] supporting the design of the current trial. While COX-2 and other inflammatory mediators are elevated in mild-to-moderate AD brain,[1] it is nonetheless possible that when the disease is clinically apparent, the neuropathology is too advanced to be significantly attenuated by NSAID therapy. The results of this trial do not address the efficacy of NSAIDs in the prevention of AD. A primary prevention trial, in which elderly persons without dementia are randomly assigned to treat-

ment with an NSAID or placebo, is necessary to test the utility of long-term NSAID therapy in AD risk reduction. Such a trial is now under way.[29]

The results of the current study do not support the hypothesis that rofecoxib or naproxen can slow the progression of AD. Considering the risk of serious toxicity, such treatment should not be recommended. In view of evidence from cell culture and animal studies suggesting reduction of β-amyloid generation with other NSAIDs, such as ibuprofen (but not naproxen or selective COX-2 inhibitors),[24] additional treatment trials using other NSAIDs may be warranted. Recommendations regarding risk reduction with long-term NSAID therapy must await the results of a primary prevention trial.

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A Randomized, Double-Blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment

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Inflammatory mechanisms have been implicated in Alzheimer's disease (AD) and might be mediated via the COX-2 enzyme. Previous studies with the selective COX-2 inhibitors, rofecoxib and celecoxib, have shown that they do not alter the progression of AD. We conducted a double-blind study to investigate whether rofecoxib could delay a diagnosis of AD in patients with mild cognitive impairment (MCI), a group with an expected annual AD diagnosis rate of 10–15%. MCI patients ≥65 years were randomized to rofecoxib 25 mg ($N=725$) or placebo ($N=732$) daily for up to 4 years. The primary end point was the percentage of patients with a clinical diagnosis of AD. The estimated annual AD diagnosis rate was lower than the anticipated 10–15%: 6.4% in the rofecoxib group vs 4.5% in the placebo group (rofecoxib : placebo hazard ratio = 1.46 (95% CI: 1.09, 1.94), $p=0.011$). Analyses of secondary end points, including measures of cognition (eg the cognitive subscale of the AD Assessment Scale (ADAS-Cog)) and global function (eg the Clinical Dementia Rating (CDR)), did not demonstrate differences between treatment groups. There was also no consistent evidence that rofecoxib differed from placebo in *post hoc* analyses comparing ADAS-Cog and CDR-sum of boxes scores in overlapping subgroups of patients who had Mini Mental State Exam scores of 24–26 in the present MCI study and in a previous AD treatment study with a similar design. The results from this MCI study did not support the hypothesis that rofecoxib would delay a diagnosis of AD. In conjunction with the lack of effects observed in previous AD studies, the findings suggest that inhibition of COX-2 is not a useful therapeutic approach in AD.

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INTRODUCTION

Neuropathological and epidemiological data suggest that inflammatory mediators and immune mechanisms may play a role in the pathogenesis of Alzheimer's disease (AD) (McGeer *et al*, 1996; Cagnin *et al*, 2001; Ho *et al*, 2001; in 't Veld *et al*, 2002; Etminan *et al*, 2003). It has been proposed that these effects may be mediated via the COX-2 enzyme (Pasinetti, 2001). These observations have led researchers to investigate whether nonsteroidal anti-inflammatory drugs (NSAIDs) might slow the progression of dementia. Initially, two small studies with the NSAIDs indomethacin (Rogers *et al*, 1993) and diclofenac (Scharf *et al*, 1999) provided preliminary evidence for efficacy over 6 months in patients with AD. However, interpretation of the results from both studies was confounded by high dropout rates, mainly due to gastrointestinal side effects thought to be mediated via inhibition of COX-1 (nonselective NSAIDs inhibit both COX-1 and COX-2) (Warner *et al*, 1999). More recently, three larger randomized, controlled, 1-year clinical studies with the selective COX-2 inhibitors rofecoxib or celecoxib failed to show any effects of treatment on the progression of AD (Sainati *et al*, 2000; Aisen *et al*, 2003; Reines *et al*, 2004). One of these studies included the nonselective NSAID naproxen, which also failed to show any effects (Aisen *et al*, 2003). In addition, the anti-inflammatory agent hydroxychloroquine did not show any benefits in an 18-month trial (Van Gool *et al*, 2001).

A possible explanation for the lack of efficacy in the above studies is that the underlying pathology might be too advanced in patients with an established diagnosis of AD for an anti-inflammatory treatment to alter the course of the disease. Epidemiological evidence indicates that there may

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be a critical period, 2 or more years before the onset of dementia, during which exposure to NSAIDs protects against AD (in 't Veld *et al*, 2001). Selective COX-2 inhibitors offer the potential for treatments that may have beneficial protective effects in AD while being well tolerated in long-term use. We therefore conducted a study to determine whether treatment with rofecoxib could delay a diagnosis of AD. Rather than evaluating a general elderly population with a relatively low incidence rate of AD, we sought to recruit elderly patients with mild cognitive impairment (MCI) (Petersen *et al*, 2001a, b). These patients were expected to have an annual AD diagnosis rate of 10–15% *vs* a rate of 1–2% for the general elderly population (Petersen *et al*, 2001a, b). The study also provided the opportunity to gather important placebo-controlled, long-term safety data on rofecoxib in an elderly population.

METHODS

Patients

Patients aged 65 years or older who had completed at least 8 grades of education, and had a reliable informant who could accompany them to each clinic visit, were recruited at 46 study sites in the United States from April 1998 to March 2000. Potentially eligible patients were initially identified by investigators (by any means available) or via a centralized telephone prescreening process (Lines *et al*, 2003). Patients were screened at the study sites to determine if they met all the following criteria for MCI: patient reports memory problem, or informant reports that patient has memory problem; informant reports that patient's memory has declined in the past year; Mini Mental State Exam (MMSE) (Folstein *et al*, 1975) score $\geqslant 24$; Clinical Dementia Rating (CDR) (Morris, 1993) global score $= 0.5$ with memory domain score $\geqslant 0.5$; Blessed Dementia Rating Scale (BDRS) (Morris *et al*, 1988) total score $\leqslant 3.5$, with no part 1 item score > 0.5; Auditory Verbal Learning Test (AVLT) (Schmidt, 1996) total score $\leqslant 37$. The cut score on the AVLT corresponds to a score $\leqslant 1$ standard deviation (SD) below the mean for normal elderly subjects; for the first 6 months of study enrollment, age-adjusted cut scores 1.5 SDs below the means for separate age bands were used (see Appendix A1). Further details of these tests of cognition and function are given in Appendix A1. The CDR assessment was completed on the basis of interviews with the patient and informant by a rater who was blinded to the results of psychometric tests (AVLT and MMSE).

Patients were excluded if they had: dementia; inadequate motor or sensory capacities to comply with testing; a modified Hachinski Ischemic Scale (Rosen *et al*, 1980) score > 4 (to exclude patients whose cognitive impairment may have been related to a vascular condition); a Hamilton Depression Scale (17-item version) (Hamilton, 1960) score > 13 (to exclude patients whose cognitive impairment may have been related to depression); a history of angina or congestive heart failure with symptoms that occurred at rest; uncontrolled hypertension; a history within the past year of myocardial infarction, coronary artery bypass, angioplasty, or stent placement; a history within the past 2 years of stroke, multiple lacunar infarcts, or transient ischemic events; a history within the past 3 months of gastrointestinal bleeding; an expected therapeutic need for chronic NSAID or estrogen replacement therapy during the study. Patients taking NSAIDs on a chronic basis ($\geqslant 7$ days/month for the 2 months prior to study entry), estrogen replacement therapy (excluding topical ointments) within 2 months of study entry, or cholinesterase inhibitors within 1 month of study entry were also excluded. No more than 20% of patients at each study site could be taking vitamin E > 400 IU at the time of study entry. Concomitant use of the above medications during the study was discouraged, but patients who did take them were not discontinued for this reason. Patients who developed a need for cardio-protective doses of aspirin after randomization were permitted to use aspirin $\leqslant 100$ mg/day; clopidogrel was also allowed. Each site received the approval of its local institutional review board to perform the study, and informed consent was obtained from each subject.

Design

This was a randomized, double-blind, placebo-controlled study with parallel groups. After screening, eligible patients were randomly assigned to receive rofecoxib 25 mg once daily or placebo once daily for up to 4 years. Rofecoxib 25 mg was the maximum recommended dose for approved chronic indications (Merck & Co. Inc., 2003; on September 30, 2004, Merck & Co. Inc., announced the voluntary worldwide withdrawal of rofecoxib from the market). Randomization of patients at each study site was determined by a computer-generated allocation schedule and was stratified according to MMSE score (24–26, > 26). The allocation schedule was generated by a statistician at Merck Research Laboratories according to in-house blinding conditions. The rofecoxib and placebo tablets were visually identical. The original intention was that the study would be event-rate driven and would continue until 220 patients had received an AD diagnosis, which it was anticipated would take approximately 2 years. The study was extended to 4 years due to lower than expected AD diagnosis rates. A decision was made in October 2002 to terminate the study in April 2003, 11 months earlier than the scheduled March 2004 termination (ie 4 years after the last patient was enrolled). Based on the diagnosis and discontinuation rates observed as of July 2002, it was estimated that 219 end points should have been observed by April 2003. In fact, only 189 diagnoses of AD had been made at this time, and discontinuation rates had continued to increase. The combination of the low diagnosis rates and increasing discontinuation rates made it unlikely that the target number of events could have been achieved and it was therefore considered that continuation of the study until its planned termination would not have been productive. The decision was made prior to unblinding.

Procedure

After randomization, patients were scheduled to attend the clinic at months 1 and 4, and then every 4 months until the study was completed or the patient was diagnosed with dementia. The study was conducted using an intent-to-treat approach; that is, patients who discontinued treatment, but who had not developed dementia, were asked to return to

the clinic for all remaining visits and assessments. The following assessments were administered at baseline and every 4 months, or at discontinuation from the study: CDR, MMSE, Selective Reminding Test (SRT; see Appendix A1 for details) (Buschke, 1973). The cognitive subscale of the AD Assessment Scale (ADAS-Cog; see Appendix A1 for details) (Rosen *et al*, 1984) was administered at baseline and then every 12 months, or at discontinuation from the study. The BDRS was administered at baseline and at 24, 36, and 48 months, or at discontinuation from the study. Any patient who received a global CDR score ≥ 1 at a routine clinic visit was suspected of having converted to dementia and administered a CT or MRI scan of the brain and any psychometric tests that were not already scheduled for that visit. The patient was continued on treatment and returned for an end point confirmation visit 2 months later, at which time all the psychometric evaluations were repeated. If the global CDR score was still ≥ 1 at this visit, the patient was considered to have reached the end point of dementia and was discontinued from the study (regardless of the outcome of the adjudication process described below). In some cases, a patient was determined by an investigator to have developed dementia despite maintaining a global CDR score of 0.5 at the trigger and confirmation visits, and these patients were also counted as end points and were discontinued from the study. The investigator determined the type of dementia: possible or probable AD according to NINCDS-ADRDA criteria (McKhann *et al*, 1984) or other, for example, vascular dementia. For patients who reached the end point of clinically diagnosed dementia, all relevant data were sent to an independent blinded adjudication committee consisting of three experts. Each adjudicator reviewed the data independently and indicated whether or not they concurred with the investigator's diagnosis. In order to qualify as an event for the primary analysis, a majority decision in ≥ 2 of the three adjudicators that the patient met criteria for possible or probable AD was required (ie ≥ 2 adjudicators classified the event as probable AD, ≥ 2 adjudicators classified the event as possible AD, or one adjudicator classified the event as possible AD and one adjudicator classified it as probable AD).

Any adverse experiences occurring during the study were recorded and rated by the investigator, while still blinded to the treatment that the patient was receiving, as to seriousness (death, life threatening, resulting in persistent or significant disability, resulting in hospitalization, prolonging an existing hospitalization, any other important medical event), drug-relatedness (possibly, probably or definitely drug-related, probably not or definitely not drug-related), and intensity (mild, moderate, or severe). All serious vascular events (including cardiac, peripheral vascular, and cerebrovascular events) and upper gastrointestinal perforations, ulcers, and bleeds were reviewed by independent blinded adjudication committees, who determined if they were confirmed events according to prespecified case definitions (confirmed events) (Bombardier *et al*, 2000; Konstam *et al*, 2001).

Statistical Analysis

The primary efficacy analysis compared the cumulative incidence of possible or probable AD according to NINCDS-ADRDA criteria (McKhann *et al*, 1984); patients with dementia of other cause were censored in the analysis at the time of diagnosis. AD diagnoses confirmed by the end point adjudication committee were the only end points included in the primary analysis. The analysis was based on a Cox proportional hazards model of time-to-event data (based on the initial diagnosis of AD) using an intention-to-treat approach, which included all randomized patients regardless of whether or not they were taking study medication. The model included terms for treatment, region within the United States (North East, South East, South, Midwest, West), and baseline MMSE strata (baseline MMSE score ≤ 26 *vs* >26). Region was intended to be a surrogate for investigating the influence of study site, since there were too few events at individual study sites to include that as a factor. An additional prespecified on-drug analysis was restricted to patients who converted to AD within 14 days of being on study medication.

The calculation for the power statement assumed that the incidence of possible or probable AD over 2 years in the placebo group would be 30% and that the discontinuation rate would be 20%. Based on these considerations and a planned sample size of 520 evaluable patients per group, the study had 90% power to detect a one-third reduction in the incidence of AD in the rofecoxib group *vs* the placebo group with two-tailed $\alpha = 0.05$.

Analyses of prespecified secondary measures (SRT-summed recall score, SRT-delayed recall score, MMSE score, ADAS-Cog score, CDR-sum of boxes score, BDRS score) were based on available data for evaluable patients (ie patients who had a baseline score and at least one postrandomization score). The annual rates of change from baseline to a given time point (slopes), and slope differences between groups, were estimated using an intention-to-treat approach (ie including all data regardless of whether a patient discontinued from therapy or not) and analyses were performed using longitudinal repeated measures models for the comparison, under the assumption that missing data were missing at random (ie ignorable missingness). Additional sensitivity analyses were also performed using a last-observation-carried forward approach, as well as with other models with different assumptions about the missing data structure.

The present study had a broadly similar design (randomized, double-blind, placebo-controlled) and utilized some similar assessments (ADAS-Cog and CDR) to a previous 1-year AD treatment study of rofecoxib 25 mg in patients who had MMSE scores of 14–26 (Reines *et al*, 2004). Since there were overlapping subgroups of patients who had MMSE scores of 24–26 in both studies, indicating a similar level of cognitive impairment despite the difference in diagnosis, we also conducted a *post hoc* analysis to compare change from baseline scores on measures of cognition (ADAS-Cog) and global function (CDR-sum of boxes) in the overlapping subgroups in the two studies. The analysis looked at estimated annual slope differences using the same methods as described above. For the subgroup from the previous AD treatment trial, the annual slope estimates were derived from data over 12 months. For the subgroup from the present study, the annual slope estimates were derived from data over 48 months.

The assessment of tolerability included on-drug adverse experiences with onset up to 14 days after patients stopped taking test medication, and was based on the population of patients who took at least one dose of study medication. Prespecified groupings of adverse experiences (eg the number of patients with one or more adverse experience) were analyzed using Fisher's exact test.

RESULTS

The study profile is shown in the study flowchart (Figure 1). A total of 1457 patients were randomized. The study was terminated after 189 confirmed diagnoses of AD had been made. The median duration of study participation was 115 weeks in the rofecoxib group and 130 weeks in the placebo group. The median duration patients took study medication was 94 weeks in the rofecoxib group and 105 weeks in the placebo group. Estimates of treatment compliance based on counts of the number of tablets in medication bottles at each clinic visit and calculated as ((number of days on therapy/number of days in study) × 100) indicated reasonable compliance; 61.0% of the 725 patients randomized to rofecoxib and 70.8% of the 732 patients randomized to placebo had ⩾80% compliance during the time they were in the study. Approximately 45% of patients discontinued the study prematurely, while 40% completed the study on-drug (including patients who had not completed 48 months of treatment but were still in the study at the time of termination), and 15% completed the study off-drug. Reasons for discontinuation were generally similar across the treatment groups, although there were some small differences; for example, a greater proportion of patients in the placebo group discontinued due to withdrawal of consent (see Figure 1). The time course of discontinuations was similar between the treatment groups over the duration

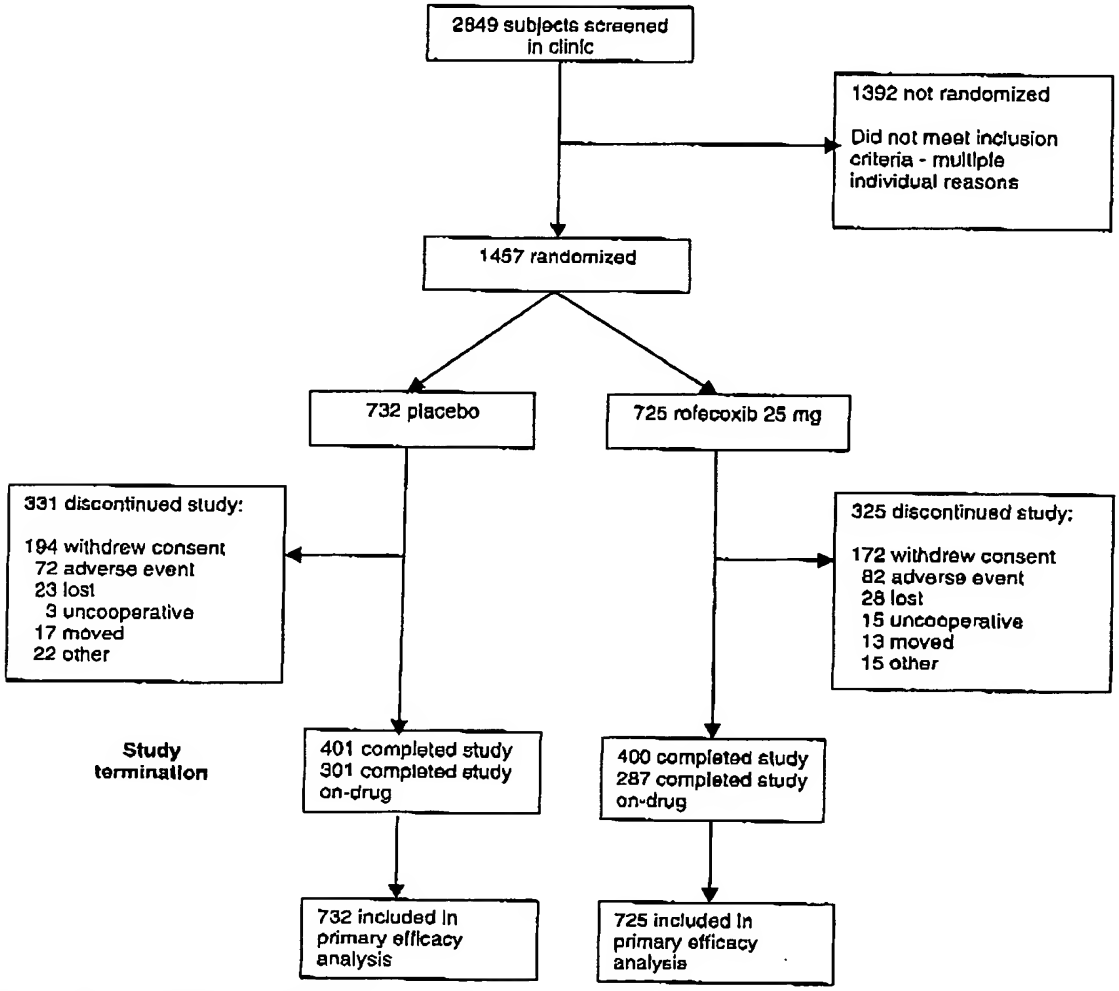

Figure 1 Study flowchart. Patients were prescreened for eligibility before being screened in the clinic. Data on the precise number of subjects prescreened were not collected, but the number was > 17 000. The total who completed the study includes patients who completed 48 months of study participation ($N = 115$ for rofecoxib, $N = 146$ for placebo), patients who were diagnosed with dementia of any cause ($N = 112$ for rofecoxib, $N = 83$ for placebo), patients who completed less than 48 months of study participation but were still in the study at the time it was terminated ($N = 121$ for rofecoxib, $N = 123$ for placebo), and patients who were discontinued because the study site closed ($N = 52$ for rofecoxib, $N = 49$ for placebo).

of the study (data not shown). Of those who discontinued, placebo patients had higher baseline ADAS-Cog scores, indicative of greater cognitive impairment and possibly greater risk of progression to AD, than patients randomized to rofecoxib ($p = 0.034$ in a logistic regression model); the mean baseline ADAS-Cog score was 9.6 in placebo discontinuers *vs* 9.1 in rofecoxib discontinuers. The change from baseline to last evaluation time point scores on the ADAS-Cog, MMSE, and CDR-sum of boxes in the subgroup of discontinued patients who had at least one on-treatment evaluation was similar between the treatment groups (data not shown).

Table 1 shows the baseline demographic characteristics and baseline test scores for randomized patients. The groups were generally comparable with regard to baseline characteristics and test scores. The distribution of secondary diagnoses at baseline was generally similar between the groups. The most common pre-existing medical conditions were hypertension (37.7% in the rofecoxib group and 34.3% in the placebo group) and osteoarthritis (22.2% in the rofecoxib group and 24.3% in the placebo group). The percentages of patients with reported prior use (for any length of time in the 2 months prior to study entry for NSAIDs and estrogen, and 1 month prior to study entry for other drugs) of drugs claimed to have an influence on dementia were generally similar in the rofecoxib *vs* placebo groups for NSAIDs (8.4 *vs* 10.2%), ginkgo (12.6 *vs* 11.2%), statins (14.9 *vs* 13.0%), estrogen (0.4 *vs* 1.4%), and vitamin E >400 IU daily (5.8 *vs* 5.6%). The percentages of patients with reported concomitant use (for any length of time during the study) of drugs claimed to have an influence on dementia were lower in the rofecoxib group than the placebo group for NSAIDs (30.9 *vs* 34.7%) and estrogen (2.6 *vs* 4.8%), higher for cholinesterase inhibitors (11.2 *vs* 8.6%), and similar for statins (24.8 *vs* 24.9%), ginkgo (13.7 *vs* 12.8%), and vitamin E >400 IU daily (7.3 *vs* 7.5%). The median duration of reported concomitant NSAID use was lower in the rofecoxib group (5.6 weeks) than the placebo group (7.4 weeks). The percentages of patients with reported aspirin use in the 2 months prior to the study were 10.1% in the rofecoxib group and 9.0% in the placebo group. The percentages of patients with reported aspirin during the study were 31.7% in the rofecoxib group and 29.9% in the placebo group.

Table 1 Baseline Patient Characteristics

Characteristic	Placebo ($N = 732$)[a]	Rofecoxib 25 mg ($N = 725$)[a]
% Women	31.1%	34.3%
% Family history of AD	29.5%	31.2%
% Apolipoprotein ε4	35.8%	34.6%
Years of education		
11 or less	9.8%	11.2%
12–17	77.7%	74.7%
18 or more	12.4%	13.4%
Mean (SD) years of age	74.8 (6.0)	75.1 (6.0)
Mean (SD) AVLT score[b]	28.6 (5.8)	28.6 (5.7)
Mean (SD) MMSE score[c]	27.3 (1.7)	27.4 (1.7)
Mean (SD) CDR-sum of boxes score[d]	1.4 (0.8)	1.4 (0.8)
Mean (SD) ADAS-Cog score[e]	9.1 (3.8)	9.2 (4.0)
Mean (SD) SRT-summed recall score[f]	33.6 (9.1)	33.4 (9.0)
Mean (SD) SRT-delayed recall score[g]	4.5 (2.9)	4.4 (2.5)
Mean (SD) BDRS score[h]	1.1 (0.7)	1.1 (0.8)

[a]Sample sizes varied for some measures due to missing data. For apolipoprotein genotyping, sample sizes were 669 for placebo and 652 for rofecoxib.
[b]Auditory Verbal Learning Test. Range = 0–75; lower score indicates greater impairment.
[c]Mini Mental State Exam. Range = 0–30; lower score indicates greater impairment.
[d]Clinical Dementia Rating. Range = 0–18; higher score indicates greater impairment.
[e]Cognitive subscale of the AD Assessment Scale. Range = 0–70; higher score indicates greater impairment.
[f]Selective Reminding Test (immediate recall component). Range = 0–72; lower score indicates greater impairment.
[g]Selective Reminding Test (delayed recall component). Range = 0–12; lower score indicates greater impairment.
[h]Blessed Dementia Rating Scale. Range = 0–17; higher score indicates greater impairment.

A total of 195 investigator diagnoses of dementia (190 diagnoses of possible or probable AD and five diagnoses of non-AD dementia) were evaluated by the end point adjudication committee. The primary end point of clinically diagnosed AD included the 189 patients who were confirmed to have developed possible or probable AD by ≥2 members of the committee. Two events adjudicated to be non-AD dementia, two events adjudicated to be nondementia, and two events in which there was no agreement between adjudicators (one adjudicator classified the event as AD, one classified it as non-AD dementia, and one classified it as nondementia) were not included as end points in the primary analysis. In the 189 patients with adjudicator-confirmed clinically diagnosed AD, global CDR scores at the last clinic visit were 0.5 (questionable dementia) in 21 patients, one (mild dementia) in 159 patients, two (moderate dementia) in eight patients, and three (severe dementia) in one patient.

In the rofecoxib group, 107 of 725 (14.8%) patients had clinically diagnosed AD over the 4-year study period *vs* 82 of 732 (11.2%) placebo patients over 4 years. The estimated hazard ratio (rofecoxib : placebo), adjusting for the effects of baseline MMSE stratum and region, was 1.46 (95% CI: 1.09, 1.94), which was statistically significant ($p = 0.011$, Wald χ^2 test) in favor of placebo. The treatment-by-time interaction was not significant ($p = 0.260$), indicating that the proportional hazards assumption was reasonably met. Baseline MMSE stratum (score ≤26; score >26) had a highly statistically significant effect on outcome with an estimated hazard ratio of 3.23 (95% CI: 2.42, 4.32) ($p < 0.001$), indicating that patients in the lower stratum were much more likely to progress to AD irrespective of treatment assignment. Treatment effects were consistent across MMSE stratum levels, as well as geographic regions. Kaplan–Meier estimated proportions of patients with clinically diagnosed AD at 4-month increments are shown in Table 2. A separation in event rates between treatment groups was evident at the earliest time point (4 months), a gap that was

Table 2 Kaplan-Meier Estimated Proportions of Clinically Diagnosed AD at 4-Month Intervals

	Placebo		Rofecoxib	
Month after treatment	N[a]	Estimated proportion	N[a]	Estimated proportion
0	732	0.0	725	0.0
4	707	0.3	682	0.9
8	666	1.4	642	3.1
12	625	3.1	582	5.1
16	581	4.2	535	7.4
20	528	6.4	486	9.2
24	458	9.2	415	12.3
28	390	10.3	344	14.2
32	359	11.0	311	15.7
36	310	12.5	258	17.9
40	240	13.7	214	19.3
44	177	15.6	159	21.0
48	86	17.4	68	23.0

[a]Number of patients at risk (number who had not been censored nor had an event up to, but not including, that time point).

maintained through the last follow-up time point of 48 months as shown by the nonsignificant p-value for the test of proportionality of treatment-specific hazard rates (see above). Estimated annual diagnosis rates were 6.4% (95% CI: 5.3%, 7.7%) in the rofecoxib group and 4.5% (95% CI: 3.6%, 5.6%) in the placebo group. The above analysis included patients whether or not they were taking study medication. In the prespecified analysis looking at events that occurred on-drug ($N=723$ for rofecoxib and $N=728$ for placebo), there was no evidence for an increased hazard ratio (1.49 (95% CI: 1.08, 2.05), $p=0.014$) compared with the hazard ratio of 1.46 observed in the primary analysis, which included patients who had stopped taking study treatment.

To further explore the unexpected finding favoring placebo in the primary analysis, we conducted a *post hoc* analysis to adjust for factors that showed an effect, at a significance level of $p<0.10$, on progression to AD. Those factors correlated with greater likelihood of progression to AD were lower baseline MMSE score stratum (24–26), female gender, age >75, and prior ginkgo use. Factors associated with a decreased risk of progressing to AD were longer duration of concomitant NSAID use, and concomitant use of statins. In the analysis that adjusted for these factors, the statistical significance of the hazard ratio was reduced (1.31 (95% CI: 0.98, 1.75) $p=0.065$). Presence of the apolipoprotein ε4 allele was a risk factor but was not included in the model because information was missing for a substantial proportion of patients. Based on a significance level of $p<0.10$, family history of AD did not appear to be a risk factor in this study.

Because rofecoxib and other NSAIDs can cause small mean increases in blood pressure (Gertz *et al*, 2002; Schwartz *et al*, 2002), and there is some evidence to suggest that increased blood pressure might be associated with an increased risk of dementia (Skoog, 1997; Birkenhager *et al*, 2001), we also performed two *post hoc* analyses to evaluate whether the rofecoxib : placebo risk ratio for diagnosis of AD increased as a function of increased blood pressure change. In the first analysis, change from baseline in mean arterial blood pressure (defined as (2 × diastolic blood pressure + systolic blood pressure)/3) at month 4 was calculated for each patient. The rofecoxib : placebo odds ratios for diagnosis of AD were then calculated for three categories of patients: those with no change or a decrease (odds ratio = 1.43), those with an increase ⩽5 mmHg (odds ratio = 1.18), and those with an increase >5 mmHg (odds ratio = 1.47). The Breslow-Day test of homogeneity of the odds ratios across categories indicated no significant differences ($p=0.895$). In the second *post hoc* analysis, we looked at a predefined limit of change in systolic blood pressure, which was prespecified as a postrandomization value that was ⩾180 mmHg and showed a ⩾20 mmHg increase from baseline. The rofecoxib : placebo hazard ratios for diagnosis of AD were similar in those patients who did not meet the predefined limit of change criteria (hazard ratio = 1.42 (95% CI: 1.06, 1.92)), compared with those who did meet the criteria (hazard ratio = 1.53 (95% CI: 0.49, 4.81)).

The least squares mean scores for the secondary end points of cognition and function at 1-year intervals using the repeated measures models approach described in Methods are summarized in Table 3. The prespecified analysis looked at the estimated annual slope difference (placebo minus rofecoxib) for each measure based on data over the entire 4-year period. In contrast to the primary end point, there were no significant differences between treatment groups on estimated annual slope differences for SRT-summed recall score (slope difference = 0.026 (95% CI: −0.307, 0.359), $p=0.878$), SRT-delayed recall score (slope difference = −0.012 (95% CI: −0.104, 0.081), $p=0.806$), MMSE score (slope difference = −0.002 (95% CI: −0.095, 0.090), $p=0.959$), ADAS-Cog score (slope difference = −0.098 (95% CI: −0.287, 0.091), $p=0.311$), or BDRS score (slope difference = 0.079 (95% CI: −0.081, 0.238), $p=0.333$). The slope difference for the CDR-sum of boxes score showed a nonsignificant trend in favor of placebo (slope difference = −0.068 (95% CI: −0.139, 0.002), $p=0.058$); this would be expected to be highly correlated with the primary end point since the global score on the CDR was used to trigger the diagnosis of AD. Additional sensitivity analyses for the secondary end points were also performed using a last-observation-carried forward approach. The results, indicating a lack of treatment differences, were similar across these analyses, which were based on different assumptions about the missing data structure.

The *post hoc* analysis comparing test scores in overlapping subgroups of patients with MMSE scores of 24–26 in the present study (the subgroup with the worst prognosis) and a previous AD treatment study (Reines *et al*, 2004) included a total of 405 patients (rofecoxib $N=189$, placebo $N=216$) from the present MCI study, and 205 patients (rofecoxib $N=91$, placebo $N=114$) from the previous AD treatment study. There was no consistent evidence of a differential treatment effect of rofecoxib in the

Table 3 Secondary End Points: Least Squares Mean (Standard Error) Scores with Difference and 95% Confidence Interval

	1-Year			2-Year			3-Year			4-Year		
Measure	Placebo[a] (N^c = 659)	Rofecoxib[a] (N^c = 624)	Difference[a,b] (95% CI)	Placebo[a] (N^c = 509)	Rofecoxib[a] (N^c = 460)	Difference[a,b] (95% CI)	Placebo[a] (N^c = 344)	Rofecoxib[a] (N^c = 302)	Difference[a,b] (95% CI)	Placebo[a] (N^c = 195)	Rofecoxib[a] (N^c = 176)	Difference[a,b] (95% CI)
SRT-summed	35.7 (0.3)	35.6 (0.4)	−0.2 (−1.1,0.7)	36.5 (0.4)	35.7 (0.4)	−0.8 (−1.9,0.3)	36.1 (0.5)	35.7 (0.5)	−0.3 (−1.7,1.1)	36.0 (0.7)	35.6 (0.7)	−0.4 (−2.3,1.5)
SRT-delayed	4.8 (0.1)	4.7 (0.1)	−0.0 (−0.3,0.2)	4.9 (0.1)	4.8 (0.1)	−0.1 (−0.5,0.2)	4.9 (0.1)	4.7 (0.1)	−0.2 (−0.6,0.1)	4.5 (0.2)	4.5 (0.2)	0.1 (−0.5,0.6)
ADAS-Cog	8.9 (0.1)	9.3 (0.1)	0.3 (−0.0,0.7)	9.4 (0.2)	9.7 (0.2)	0.3 (−0.3,0.8)	9.8 (0.3)	10.1 (0.3)	0.3 (−0.4,1.0)	10.3 (0.3)	10.7 (0.3)	0.3 (−0.4,1.1)
MMSE	27.3 (0.1)	27.2 (0.1)	−0.1 (−0.3,0.1)	27.2 (0.1)	27.3 (0.1)	0.1 (−0.2,0.4)	27.1 (0.1)	27.1 (0.1)	−0.1 (−0.4,0.3)	26.7 (0.2)	26.5 (0.2)	−0.2 (−0.7,0.3)
CDR-sum of boxes	1.5 (0.0)	1.6 (0.0)	0.1 (−0.0,0.2)	1.8 (0.1)	2.0 (0.1)	0.2 (−0.0,0.4)	2.1 (0.1)	2.2 (0.1)	0.2 (−0.0,0.4)	2.2 (0.1)	2.4 (0.1)	0.2 (−0.0,0.5)
BDRS	—	—	—	1.4 (0.1)	1.4 (0.1)	0.0 (−0.1,0.2)	1.4 (0.1)	1.5 (0.1)	0.1 (−0.1,0.3)	1.4 (0.1)	1.6 (0.1)	0.1 (−0.1,0.4)

[a]Results based on repeated measures model.
[b]Difference is rofecoxib−placebo.
[c]Sample size (number of patients with any secondary efficacy measure by time point).
See Table 1 for key to test abbreviations and interpretation of direction of scores. 1-year data are not provided for the BDRS because it was not scheduled to be administered until the 2-year time point.

overlapping subgroups in the two studies. The estimated annual slope difference for the ADAS-Cog score was −0.240 (95% CI: −0.736, 0.255), $p = 0.340$ in the MMSE 24–26 subgroup from the present study, and 0.447 (95% CI: −1.284, 2.178), $p = 0.611$ in the MMSE 24–26 subgroup from the previous AD treatment study. The estimated annual slope difference for the CDR-sum of boxes score was −0.180 (95% CI: −0.350, −0.009), $p = 0.039$ in the MMSE 24–26 subgroup from the present study, and −0.053 (95% CI: −0.560, 0.454), $p = 0.837$ in the MMSE 24–26 subgroup from the previous AD treatment study.

A total of 1451 patients were included in the on-drug safety analysis (723 in the rofecoxib group and 728 in the placebo group). There were slightly fewer patients in the safety analysis than in the efficacy analysis because six patients who never took study medication were excluded from the safety analysis. The adverse experience profile is summarized in Table 4. The rofecoxib and placebo groups were similar with regard to the percentages of patients with any adverse experience, any serious adverse experience, and who discontinued treatment due to an adverse experience. There was a significant increase for rofecoxib in the number of patients with adverse experiences that were considered possibly, probably, or definitely drug-related by the investigators. The most common drug-related adverse experiences are shown in Table 4. There was no particular individual adverse experience that contributed to the overall difference between rofecoxib and placebo for drug-related adverse experiences, and relatively few patients discontinued study treatment due to drug-related adverse experiences (58 or 8.0% for rofecoxib and 41 or 5.6% for placebo). The number of patients with confirmed upper gastrointestinal perforations, ulcers, or bleeds was 14 in the rofecoxib group and four in the placebo group. A total of 39 deaths occurred in patients who were taking study treatment or from fatal adverse events that started within 14 days of the last dose (24 or 3.3% for rofecoxib and 15 or 2.1% for placebo). Patients died from a range of causes that were consistent with expectations for an elderly population, and there was no specific pattern as to the cause of death in either treatment group. The only specific fatal adverse events with more than one patient per treatment group were myocardial infarction (four patients on rofecoxib and three on placebo), cardiac arrest (two patients on rofecoxib and none on placebo), pneumonia (two patients on rofecoxib and none on placebo), and renal failure (one patient on rofecoxib and two on placebo). (An individual patient may have had more than one adverse event associated with death.) Off-drug follow-up mortality data were available for less than half of the patients ($N = 356$ for rofecoxib, $N = 307$ for placebo); the median duration of off-drug follow-up in these patients was 29 weeks in the rofecoxib group and 20 weeks in the placebo group. There were an additional 22 deaths in the off-drug period (17 in patients assigned to rofecoxib and five in patients assigned to placebo); 12 of these (11 in the rofecoxib group and one in the placebo group) occurred more than 48 weeks after treatment discontinuation. Compared with the on-drug period, there were an additional five patients with off-drug myocardial infarction fatal adverse events (five rofecoxib, none placebo), and an additional two patients with each of cardiac arrest (two rofecoxib, none placebo), pneumonia

Table 4 Summary of Clinical Adverse Experiences

Number (%) of patients with	Placebo ($N=728$)	Rofecoxib 25 mg ($N=723$)
⩾1 adverse experience	670 (92.0%)	651 (90.0%)
⩾1 drug-related adverse experience[a]	173 (23.8%)	211 (29.2%)*
Serious adverse experience[b]	236 (32.4%)	217 (30.0%)
Discontinued treatment due to adverse experience	147 (20.2%)	156 (21.6%)
Most common drug related adverse experiences[c]		
Diarrhea	16 (2.2%)	11 (1.5%)
Dyspepsia	17 (2.3%)	24 (3.3%)
Nausea	15 (2.1%)	14 (1.9%)
Dizziness	14 (1.9%)	18 (2.5%)
Peripheral edema	11 (1.5%)	23 (3.2%)
Increased blood pressure	14 (1.9%)	16 (2.2%)
Hypertension	25 (3.4%)	29 (4.0%)

[a]Experiences that were rated as possibly, probably, or definitely drug-related by the investigator.
[b]Death, cancer, any adverse event that was life threatening, resulted in persistent or significant disability, resulted in or prolonged an existing hospitalization, or any other important medical event.
[c]Incidence >2.0% in either treatment group.
*Significantly different from placebo, $p<0.05$.

(two rofecoxib, none placebo), and renal failure (two rofecoxib, none placebo) off-drug fatal adverse events. The number of patients with confirmed serious thrombotic vascular events on-drug was similar in the two groups (38 in the rofecoxib group and 36 in the placebo group). There were a total of six patients with confirmed ischemic strokes and one patient with hemorrhagic stroke in the rofecoxib group compared to 13 patients with confirmed ischemic strokes and two patients with hemorrhagic strokes in the placebo group. Thirteen patients in the rofecoxib group had confirmed nonfatal myocardial infarctions *vs* 10 in the placebo group.

DISCUSSION

In this 4-year study of 1457 patients with MCI, there was no evidence that rofecoxib delayed a diagnosis of AD. A treatment difference in favor of placebo was observed on the primary end point of time to clinically diagnosed AD. This finding was not confirmed by secondary measures of cognition (ADAS-Cog, SRT, MMSE) or global function (BDRS, CDR-sum of boxes), which found no statistically significant or clinically meaningful differences between treatment groups. The possibility that rofecoxib might be inferior to placebo was also not supported by data from two large previous AD treatment studies, which included patients with an MMSE score up to 26 (thereby partly overlapping with patients in the present study who had an MMSE score ⩾24), and found that rofecoxib had no significant effect on the progression of cognitive or functional decline (Aisen *et al*, 2003; Reines *et al*, 2004).

Given the unexpected nature of the primary finding, it was thought important to compare the present results with those from an independent database. We therefore conducted a *post hoc* analysis of test scores in subgroups of patients with MMSE scores of 24–26 in the present study (ie those patients who were most likely to receive a diagnosis of AD) and in a previous AD treatment study (Reines *et al*, 2004). These studies had similar designs and utilized similar assessments. Since MCI is hypothesized to be on a continuum of cognitive impairment ranging from very mild impairment (ie MCI) through mild, moderate, and severe dementia, it is plausible that many patients with MMSE scores of 24–26 in the two studies may have been biologically similar, even though one group was diagnosed with dementia and the other was not. There was no evidence to suggest differences between treatments on assessments of cognition (ADAS-Cog) in this subgroup in either study. In the subgroup analysis from the present study, there was a significant difference between treatments for the CDR-sum of boxes score. This finding was not surprising given that the global score on the CDR was the trigger for diagnosing AD. Indeed, because of its close relation with the primary end point of AD diagnosis, the CDR sum-of boxes score can be viewed as a surrogate for the primary end point. There was no difference between rofecoxib and placebo on the CDR sum-of-boxes score in the subgroup analysis from the previous AD treatment study.

An intriguing observation in the present study was that the separation between treatment groups in rates of diagnosis of AD was apparent from 4 months (the earliest time point assessed) but did not increase over time, raising the possibility that there may have been an imbalance between the groups at baseline. Although there was no clear evidence of a major imbalance for measured baseline variables, including severity of impairment, the model which adjusted for covariates that were risk factors for receiving a diagnosis of AD showed the smallest treatment effect and was not statistically significant. The finding that the treatment difference was not further increased in the analysis restricted to the on-drug population was also not supportive of a true treatment effect.

Since this is the first report of a completed randomized controlled study examining progression to an AD diagnosis in MCI patients, it is important to consider aspects of the design or conduct of the study that could have had an influence on the results. An obvious concern in a study with a long duration is that differential discontinuation rates may have influenced the results. A discontinuation rate of approximately 45% occurred over the course of the study and only 40% of patients completed the study on-drug. These findings are not surprising given the duration of the study and the elderly population being investigated. Overall discontinuation rates, time course of discontinuations, and change from baseline test scores at the time of discontinuation were similar between the treatment groups, although there were some small differences between the groups with regard to specific reasons for discontinuation; for example, a greater proportion of patients in the placebo group discontinued due to withdrawal of consent. The relatively high proportion of patients who withdrew consent may have been a consequence of the fact that patients were required to sign an additional consent form after 2 years,

owing to the study being extended beyond the original timeline, and were unwilling to go beyond their initial commitment. There was also some evidence that patients who discontinued from the placebo group were more impaired at baseline on the ADAS-Cog than patients who discontinued from the rofecoxib group. If the more impaired patients who discontinued were at higher risk of conversion to AD, then differential dropouts may have had an influence on the results.

Another notable observation in the present study was that the overall annual AD diagnosis rate of 5–6% was lower than the anticipated 10–15% annual diagnosis rate reported in previous observational or natural history studies (Petersen *et al*, 2001a, b). There are several possible explanations for this disparity. Firstly, the diagnosis of MCI is heavily dependent on clinical judgment (Petersen, 2003), and the particular tests and score thresholds used to provide objective evidence of memory impairment are not standardized (Chertkow, 2002; Petersen, 2003). It is therefore possible that the population of patients included in the study was more heterogenous than, or different from, MCI populations previously described. Indeed, the population contained a lower proportion of women and patients with the apolipoprotein ε4 allele than others have reported (Petersen *et al*, 1999; Jack *et al*, 1999; Morris *et al*, 2001). Another possible contributing factor to the low diagnosis rates was the change in the cut-score criteria on the AVLT (the memory test used to provide objective evidence of memory impairment) during the study. After 6 months of enrollment, the cutoff was changed from age-adjusted 1.5 SD cut scores to a single cut score 1 SD below the mean for normal elderly subjects (see Appendix A1). We retrospectively looked at diagnosis rates in patients who met the original 1.5 SD criteria ($N=203$ for rofecoxib and $N=203$ for placebo) and the estimated annual diagnosis rates (11.3% for rofecoxib and 8.3% for placebo) were more in line with previous data, although still lower than anticipated for the placebo group. Finally, the fact that the MCI concept was relatively new at the time the study was initiated, along with the source of the patients (advertising campaigns as well as direct clinical referrals), may have also resulted in greater heterogeneity with regard to underlying etiology in the recruited patients.

To summarize the efficacy data, the unexpected primary finding in the present study suggesting that rofecoxib might accelerate the rate of AD diagnosis in patients with MCI was not supported by data on secondary measures in the same study, nor by other data from previous studies that assessed cognitive and functional decline in AD patients (Aisen *et al*, 2003; Reines *et al*, 2004). These observations suggest that the finding may not be indicative of a true treatment effect. If not a true effect, then the most likely explanations are a chance occurrence, or an imbalance between the treatment groups that existed at baseline or arose during the study due to differential discontinuations.

We cannot exclude the possibility that rofecoxib might accelerate conversion of MCI patients to AD, although this possibility would be at variance with the prior epidemiological and clinical data cited above, as well as the body of experimental evidence suggesting that COX-2 inhibition might attenuate neuronal death in several disease states including Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis, in addition to AD (Andreasson *et al*, 2001; Jain *et al*, 2002; Xiang *et al*, 2002; Giovannini *et al*, 2003; Scali *et al*, 2003; Teismann *et al*, 2003; Qin *et al*, 2003; Consilvio *et al*, 2004; Rose *et al*, 2004). The early onset of the treatment difference (and the lack of progressive widening of the difference over the course of the trial) further argues against a direct effect of rofecoxib on the underlying pathophysiology in AD. It could be speculated that the apparent increased conversion to AD might be secondary to a non-AD-specific aspect of rofecoxib's biological effects. For example, rofecoxib and other NSAIDs can cause small mean increases in blood pressure (Gertz *et al*, 2002; Schwartz *et al*, 2002). It has been suggested that increased blood pressure might be associated with an increased risk of dementia, although the evidence is inconsistent (Skoog, 1997; Birkenhager *et al*, 2001). We investigated this possibility by performing *post hoc* analyses to determine if the rofecoxib : placebo risk ratio for diagnosis of AD increased as a function of increased blood pressure change. There was no evidence for such a relationship. A proposed mechanism by which increased blood pressure could lead to dementia is due to an increased risk for cardiovascular adverse events such as strokes or infarcts. As noted below, there was no evidence for an increase in these types of events in patients taking rofecoxib. Furthermore, CT or MRI brain scans were performed in all patients diagnosed with dementia, to exclude the possibility of vascular dementia.

In addition to evaluating efficacy, the present study provided important placebo-controlled data on the safety of rofecoxib 25 mg over periods of up to 4 years in an elderly population. The median duration of exposure to study medication was approximately 2 years. The mean age of patients was 75 years and approximately 50% were at least 75 years old. Previous safety data on rofecoxib come largely from osteoarthritis studies looking at a relatively younger population with a mean age around 60 years (Langman *et al*, 1999; Reicin *et al*, 2002). Rofecoxib was generally well tolerated by the elderly patients in the study, consistent with results from prior clinical studies in osteoarthritis (Langman *et al*, 1999; Reicin *et al*, 2002) and AD (Reines *et al*, 2004). The overall incidence of adverse experiences, serious adverse experiences, and discontinuations due to adverse experiences were similar or only slightly increased for rofecoxib *vs* placebo. Not surprisingly, there was an increase in the number of adverse experiences thought to be drug-related by the investigators for rofecoxib *vs* placebo, but relatively few patients discontinued treatment due to these adverse experiences. The increase was mainly due to small increases in adverse experiences known to be associated with NSAID use and previously reported for rofecoxib such as dyspepsia, hypertension, and peripheral edema. Despite the high mean age of the study population, few patients had confirmed upper gastrointestinal perforations, ulcers, or bleeds, although there were numerically more in the rofecoxib group than in the placebo group. Elderly patients are at increased risk for serious vascular events. Rofecoxib did not appear to increase the risk in this study, since the number of confirmed serious thrombotic vascular events was similar in each treatment group. The procedure used for determining confirmed cardiovascular events, such as heart attack and stroke, was the same as for the recent

3-year APPROVe (Adenomatous Polyp Prevention on Vioxx) study in 2586 patients (62% male, mean age 59 years) with a history of colorectal adenomas, which found an approximately two-fold increased relative risk for these events in patients taking rofecoxib *vs* placebo, beginning after 18 months of treatment (Bresalier *et al*, 2004). The reason for the discrepancy between the present findings and those from APPROVe is unclear. No striking differences were noted between the treatment groups with regard to other, nonserious, vascular adverse events in the present study. The total number of deaths and causes of death on-drug were consistent with expectations for an elderly population, and there was no specific pattern as to the cause of death in either treatment group. The off-drug mortality data are difficult to assess since follow-up information was available for less than half the patients, there was an imbalance in the extent of follow-up data between the two groups, and the majority of deaths occurred more than 48 weeks after treatment had been discontinued.

In conclusion, the finding that rofecoxib did not delay a diagnosis of AD in the present study, or slow the progression of AD in previous studies (Aisen *et al*, 2003; Reines *et al*, 2004), suggests that inhibition of COX-2 is not a useful therapeutic approach in AD. It is possible that nonselective NSAIDs may still be found to have beneficial effects in treating or delaying the progression of symptoms in AD, due to factors other than COX-2 inhibition. However, the only long-term results from an adequately designed study with a nonselective NSAID (naproxen) available to date are not encouraging (Aisen *et al*, 2003). Trials evaluating alternative, non-anti-inflammatory, approaches to delaying a diagnosis of AD in patients with MCI are underway (Petersen, 2003).

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APPENDIX A1

Details of Tests Used

MMSE (Folstein *et al*, 1975): This is a brief test of overall cognitive function (range of scores = 0–30, lower score indicates greater impairment). Patients who scored <24 were excluded because of the possibility that they might have dementia.

AVLT (Schmidt, 1996): This is a 15-item, five-trial, word recall test (range of scores = 0–75, lower score indicates greater impairment). The interference trial and delayed recall trial, which usually follow the initial five-trial learning phase, were not administered. Patients had to score $\leqslant 37$ words recalled correctly over five trials as objective evidence of memory impairment. This corresponds to a score $\leqslant 1$ SD below the mean for normal elderly subjects aged 65–69 (Ivnik *et al*, 1990). For the first 6 months of study enrollment, age-adjusted cut scores 1.5 SDs below the means for separate age bands were used (eg there was a cut score for those aged 67–69, another cut score for those aged 70–72, etc), but the criteria were modified after 6 months due to concerns that the original criteria may have been too strict and were conflicting with investigator's clinical judgment (see Petersen, 2003), resulting in low enrollment.

CDR (Morris, 1993): This is a global dementia rating scale, based on a semistructured interview with the patient and an informant. Patients are rated on dementia severity (0 = none, 0.5 = questionable dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia) in six domains or 'boxes' (memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care). The global CDR score (range = 0–3, higher score indicates greater impairment) was determined according to a computerized version of the published scoring algorithm (http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html). The sum of scores on the individual boxes was also calculated (range = 0–18, higher score indicates greater impairment). Patients had to have a global CDR score of 0.5 (questionable dementia) with a score of at least 0.5 in the memory domain to qualify for study entry.

ADAS-Cog (Rosen *et al*, 1984): This consists of 11 performance-based subtests of cognition, including measures of memory and praxis. The error scores on each subtest are added to give the total score (range = 0–70, higher score indicates greater impairment).

SRT (Buschke, 1973): This is a 12-item, six-trial, word list recall test with selective reminding of words not correctly recalled on the immediately preceding trial. Following the sixth trial, there is a 5 min delay, after which the patients are again asked to recall the list of 12 words. Two scores were derived—the sum of the number of words recalled over each of the six selective reminding trials (SRT-summed recall: range = 0–72, lower score indicates greater impairment) and the number of words recalled after the 5 min delay (SRT-delayed recall; range = 0–12, lower score indicates greater impairment).

BDRS (Morris *et al*, 1988): The version from the CERAD battery was used. This is an informant-based rating of a patient's ability to perform activities of daily living such as household tasks (Part 1) and self-care (Part 2) (range of scores = 0–17, higher score indicates greater impairment). Patients who scored >3.5 with any Part 1 item score >0.5 (indicating severe impairment) were excluded because of the possibility of dementia.

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Subjective Memory Deterioration and Future Dementia in People Aged 65 and Older

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OBJECTIVES: To study whether subjective memory deterioration is associated with future dementia in older people.

DESIGN: A population-based prospective cohort study begun in 1994 with biennial follow-up interviews.

SETTING: Community-based members of Group Health Cooperative, a large health maintenance organization in the Seattle area.

PARTICIPANTS: A sample of 1,883 subjects, dementia free, aged 65 and older, who scored 91 or higher on the 100-point Cognitive Ability Screening Instrument (CASI) at study entry.

MEASUREMENTS: Subjective memory was assessed by asking whether memory had changed on 5-point Likert scales (e.g., 1 = definitely improved, 3 = no change, 5 = definitely deteriorated) with regard to five items: remembering names, faces, friends, and appointments and judging the time. The items were summed for a possible total score ranging from 5 to 25. Subjective memory deterioration was defined as present if the total score was 20 or above. Cognitive performance was measured using the CASI. Incident dementia cases were identified using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria.

RESULTS: Of 1,883 subjects, 126 developed dementia during 5 years of follow-up. Subjective memory deterioration was associated with cognitive decline and incident dementia. Age modified the association between subjective memory deterioration and future dementia. For persons reporting subjective memory deterioration at the ages of 70, 75, and 80, the hazard ratios of developing dementia were 6.0 (95% confidence interval (CI) = 2.1–18), 3.2 (95% CI = 1.6–6.2) and 1.6 (95% CI = 0.86–3.1), respectively.

CONCLUSION: Subjective memory deterioration was found to precede the development of dementia in older people with normal cognitive screening results. These findings suggest that a high level of subjective memory deterioration in persons with normal objective cognitive function may identify a subset of individuals at greater risk for developing dementia. J Am Geriatr Soc 52:2045–2051, 2004.

Key words: subjective memory deterioration; incident dementia

The introduction of interventions to slow down the development of Alzheimer's disease (AD) and other types of dementia stresses the need to detect dementia at an early stage. Therefore, it is important to search for early signs of dementia. Many older people report subjective memory decline or so called memory complaints.[1–4] Self-perceived memory deterioration may be a harbinger of future dementia in older people.

Development of dementia, particularly AD, often follows a gradual course that may take years before clinical dementia can be observed. During its course, people might perceive their own cognitive decline, manifested as memory deterioration, at an early period when they still appear normal, but it is unknown whether, and to what extent, self-perceived decline is a perception of the normal aging process or might represent an early sign of dementia.

Several population-based longitudinal studies found that subjective memory complaints were associated with cognitive decline or dementia,[4–10] but other studies found no association.[11,12] Most of these studies included individuals with evidence of objective cognitive impairment and therefore were unable to address the question of whether subjective memory complaints were a sign of future dementia at an early stage when objective impairment was not evident. Few studies have investigated the temporal relationship between subjective memory complaints and future dementia in nondemented older people who had no objective evidence of cognitive impairment on a screening test. Only two reports, both from the Amsterdam Study of the

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Elderly (ASE), found that memory complaints were associated with incident AD[7] and accelerated cognitive decline[9] in older people in whom cognitive impairment was not yet apparent. In the ASE, memory complaints were assessed using a general question regarding whether a person had complaints about memory. The question assessed the prevalence of memory problems, but people could complain about their memory for reasons that were not necessarily related to worsening in memory.[13,14] By contrast, the current study focused on perceived change in memory as assessed using five specific questions about whether a person's memory had changed, because perceived worsening in memory might be an early sign in the development of dementia with insidious onset like AD. It was hypothesized that a high level of self-perceived memory decline is associated with future dementia in older people whose cognition was in the normal range at baseline.

METHODS

Subjects

The subjects were selected from the Adult Changes in Thought (ACT) study. The study design of the ACT has been described in more detail elsewhere.[15,16] In brief, the study population was sampled from Group Health Cooperative members aged 65 and older in the Seattle area from 1994 to 1996. Subjects received the Cognitive Ability Screening Instrument (CASI)[17] as the initial cognitive screen and were interviewed with structured questionnaires to obtain data on demographics, medical history, memory and general functioning, and potential epidemiological risk factors. The CASI provides quantitative assessment of attention, concentration, orientation, short-term memory, long-term memory, language ability, visual construction, list-generating fluency, abstraction, and judgment.[17] The CASI score ranges from 0 to 100. Scores of the Mini-Mental State Examination and the modified Mini-Mental State Examination can also be estimated from subsets of the CASI items.[17] Subjects scoring 86 or higher were directly entered into the ACT cohort as cognitively intact. Those with a score lower than 86 or an invalid CASI score underwent additional medical record review and further evaluation. Those who did not meet established criteria for dementia[18] were included in the ACT inception cohort. Of a random sample of 6,782 subjects, 1,360 were incligible because they were current residents of a nursing home, were participating in another research study, had existing dementia, or met criteria for dementia as a result of screening and examinations. Of 5,422 eligible subjects, 2,841 chose not to participate for a variety of medical, personal, and other reasons before they were formally approached and asked for consent; 2,581 enrolled in the study. Nonresponse has been described elsewhere.[15] Briefly, refusal was more common in the oldest age group (≥ 85), women, and African-American and minority groups. Dementia and AD incidence rates from the ACT study have been published. These rates were in accordance with rates reported in U.S. and European cohort studies.[15]

The present study sample was selected from the 2,581 ACT participants. One thousand eight hundred ninety-four subjects whose CASI scores were above the 25th percentile (CASI scores 91–100) were selected. Six hundred eighty-seven subjects whose CASI scores were in the lowest quartile (CASI scores 62–90 or invalid scores) were excluded because the lowest quartile group might include subjects who had cognitive impairment or impending dementia, and thus, it could not be ascertained that subjective memory deterioration preceded the development of dementia in this group. Eleven subjects who did not have baseline data on subjective memory change were also excluded. Of 1,883 subjects included in this study, 1,739 had at least one follow-up visit; 144 died or discontinued right after their baseline visits.

Incident Dementia

Biennial examinations were conducted to identify incident dementia cases. Subjects were rescreened using the CASI at biennial examinations. Those who scored 86 or higher on the CASI remained in the ACT cohort. CASI scores of less than 86 at follow-up triggered a full standardized clinical examination. The results of rescreening using the CASI and the clinical examination were reviewed at a consensus diagnosis conference that included at least the examining physician, a neuropsychologist, another study physician, and the study nurse. Subjects who did not meet the criteria for dementia remained in the ACT cohort, receiving follow-up with biennial examinations, whereas subjects who met the criteria for dementia were considered as incident dementia cases and were followed annually to confirm the accuracy of the dementia diagnosis. Subjects who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria[18] for dementia were considered incident dementia cases. Dementia type was determined using the National Institute of Neurological and Communicative Disease and Stroke/Alzheimer's Disease and Related Disorder Association criteria[19] for AD and DSM-IV criteria[18] for other types of dementia.

Cognitive Function

Overall cognitive ability was measured using the CASI. Memory performance was measured using the short-term memory recall (STM), which is the three-word recall within the CASI test. Cognitive decline was defined as a drop in CASI scores to 86 or lower at follow-up, because the cutoff CASI score value of 86 was the threshold used to trigger clinical examinations.

Assessment of Subjective Memory Change

Subjective memory change, as a part of memory and functioning evaluation, was assessed using five items. "In the past 10 to 20 years or since the last visit, do you think: (1) Your ability to remember the names of people you have just met has changed? (2) Your ability to remember the faces of people you have just met has changed? (3) Your ability to remember the names of close friends or relatives has changed? (4) Your ability to remember appointments correctly has changed? (5) Your ability to judge the passage of time and guessing the time of day without looking at a clock or the sun has changed?" Response categories for each item were 1 = definitely improved, 2 = slightly improved, 3 = no change, 4 = slightly deteriorated, and 5 = definitely deteriorated. The Subjective Memory Rating Scale (SMRS) was composed by summing the five items and ranged from 5 to 25. A score of 15 on the SMRS indicated no change on

average, and a score of 20 indicated slight deterioration in all items on average. Subjective memory deterioration was defined as an SMRS score of 20 and above.

Other Variables

Demographic variables were age, sex, ethnicity, and years of education. Family history of AD was defined as having a first-degree relative (parent or sibling) with AD. Depression was measured using the 11-item Center for Epidemiologic Studies Depression Scale (CES-D)[20] at baseline. CES-D scores ranged from 0 to 33, with higher scores representing more depressive symptoms. A blood sample was drawn from consenting subjects at baseline to obtain apolipoprotein E (ApoE) genotype.

Data Analysis

Cronbach alpha test was performed to assess the internal consistency of the SMRS. Exploratory factor analysis was used to describe relationships between the five memory items.

Because many factors, such as depression,[2–4,6,9] education level,[2,15] ApoE genotype,[9,21] and a family history of AD, could confound self-reported subjective memory, confounders needed to be examined and adjusted. Therefore, logistic regression was used to examine factors that might be associated with subjective memory deterioration at baseline. The analysis used the factors age; sex; years of education; family history of AD; ApoE genotype; and baseline CES-D, CASI, and STM scores.

To investigate whether subjective memory deterioration was associated with cognitive decline, logistic regression was performed using cognitive decline as the response variable. Not only the temporal relationship of subjective memory deterioration preceding cognitive decline, but also the co-occurrence of subjective memory deterioration and performance decline was examined to assess the validity of subjective memory deterioration. In this analysis, subjective memory deterioration was classified as subjective memory deterioration at baseline or new subjective memory deterioration at follow-up. The variables adjusted for were age; sex; years of education; family history of AD; ApoE genotype; and baseline CES-D, CASI, and STM scores.

To evaluate the temporal relationship between subjective memory deterioration and incident dementia, Cox regression was performed using years of age for the time scale, left truncated at age of entry into the study. The outcome of interest was the time from the age of entry into the study to the age of dementia. The predictor of interest was subjective memory deterioration at baseline. Hazard ratios (HRs) in the Cox model were calculated at years of age during the study. Because onset of clinical dementia, particularly AD, is not a discretely timed event, it could only be determined that a subject developed dementia during the study period between the time of dementia diagnosis and the previous examination. The halfway point between diagnosis and the previous examination was taken as the event time for dementia. Subjects who died or discontinued the study before developing dementia were considered censored at the last visit date. Subjects who did not develop dementia during the study were considered censored at the last follow-up date. Variables adjusted for were baseline cognitive performance, ApoE genotype, family history of AD, baseline CES-D scores, sex, and education. The Schoenfeld residual test[22] was used to check the proportional hazard assumption. If the assumption failed, time-varying covariates were introduced.

To investigate potential effect modifications, the interactions between subjective memory deterioration and other covariates were tested in these regression models. Effect modification was considered to be present if the coefficient for the interaction was found to be statistically significant at $P = .05$.

RESULTS

Study participants were followed from 1994 to 2002, with a mean ± standard deviation follow-up of 5.2 ± 2.1 years. Of 1,883 subjects, 1,288 remained dementia free, 326 died, 143 dropped out, and 126 developed dementia (83 AD). Table 1 shows the baseline characteristics of study participants who remained dementia free, developed dementia, dropped out or died. Table 2 shows the baseline characteristics of study population by levels of subjective memory deterioration.

Over 5 years of follow-up, 15% of persons with baseline subjective memory deterioration developed dementia, in comparison with 13% of persons with family history of AD and 11% of persons with ApoE e3/4 or e4/4 alleles. By contrast, dementia occurred in 6% of persons without baseline subjective memory deterioration, 6% of persons without family history of AD, and 6% of persons with ApoE e3/3 alleles.

The SMRS had a Cronbach alpha coefficient of 0.6. Exploratory factor analysis found one common factor with an eigen value greater than 1 and factor loadings from 0.4 to 0.5 for the five items of remembering names, faces, friends and relatives, and appointments and judging time.

Factors associated with subjective memory deterioration at baseline were older age, male sex, high CES-D scores, and presence of the ApoE e2/4 alleles. Odds ratios of subjective memory deterioration for 5-year increments of age, male sex, one-point increase of CES-D score, and presence of ApoE e2/4 alleles versus e3/3 alleles were 1.28 (95% confidence interval (CI) = 1.07–1.54), 1.96 (95% CI = 1.24–3.10), 1.10 (95% CI = 1.06–1.15), and 3.14 (95% CI = 1.10–8.99), respectively. Baseline subjective memory deterioration was not associated with performance on the cognitive and memory tests using CASI and STM. Although it was expected that a family history of AD might lead to concerns about memory deterioration, the data showed that family history of AD was not associated with subjective memory deterioration.

Subjective memory deterioration was associated with cognitive decline at follow-up. Of 1,739 subjects who had been followed, 1,599 reported no subjective memory deterioration at baseline and follow-up, 79 reported subjective memory deterioration at baseline, and 61 reported new subjective memory deterioration at follow-up. During follow-up, 202 subjects declined in their cognitive performance, with a drop in CASI score to 86 or lower: 165 (10.3%) of those without subjective memory deterioration, 21 (34.4%) of those with subjective memory deterioration at follow-up, and 16 (20.3%) of those with subjective memory deterioration at baseline. Odds ratios of cognitive decline

Table 1. Baseline Characteristics of Study Participants by Follow-Up Status

Baseline Variables	Nondemented (n = 1,288; 68%)	Demented (n = 126; 7%)	Dropped Out or Died (n = 469; 25%)	Total (N = 1,883; 100%)
Age, mean ± SD	73.5 ± 5.2	78.4 ± 5.5	76.5 ± 6.6	74.6 ± 5.8
Sex, n (%)				
Male	489 (64)	55 (7)	215 (28)	759
Female	799 (71)	71 (6)	254 (23)	1,124
Ethnicity, n (%)				
White	1,208(68)	122 (7)	442 (25)	1772
Nonwhite	79 (72)	4 (4)	27 (25)	110
Education, years				
<12, n (%)	93 (57)	12 (7)	57 (35)	162
≥12, n (%)	1,193 (69)	113 (6)	412 (24)	1,718
Mean ± SD	14.3 ± 2.7	14.3 ± 2.8	13.9 ± 2.9	14.2 ± 2.7
Apolipoprotein E alleles, n (%)				
e3/3	738 (70)	61 (6)	254 (24)	1,053
e2/4	28 (82)	3 (9)	3 (9)	34
e2/2 or e2/3	169 (69)	8 (3)	68 (28)	245
e3/4 or e4/4	242 (64)	43 (11)	96 (25)	381
Missing	111 (65)	11 (6)	48 (28)	170
Family history of Alzheimer's disease, n (%)				
No	1,207 (68)	110 (6)	451 (26)	1,768
Yes	82 (71)	15 (13)	18 (16)	115
Subjective memory rating scale (5–25)				
≤15, n (%)	373 (70)	26 (5)	44 (8)	536
16–19, n (%)	865 (69)	87 (7)	90 (7)	1,260
≥20, n (%)	50 (57)	13 (15)	9 (10)	87
Score, mean ± SD	16.4 ± 1.7	16.9 ± 2.0	16.3 ± 2.1	16.4 ± 1.8
Short-term memory recall score (0–12)				
≤9, n (%)	122 (57)	29 (14)	14 (7)	214
10–12, n (%)	1,166(70)	97 (6)	129 (8)	1,669
Mean ± SD	11.1 ± 1.1	10.5 ± 1.4	10.9 ± 1.1	11.0 ± 1.2
Cognitive ability screening instrument score (0–100)				
91–93, n (%)	309 (59)	50 (10)	56 (11)	520
94–97, n (%)	676 (68)	64 (6)	65 (7)	988
98–100, n (%)	303 (81)	12 (3)	22 (6)	375
Mean ± SD	95.4 ± 2.4	94.3 ± 2.3	94.7 ± 2.3	95.2 ± 2.4
Depression				
Center for Epidemiologic Studies Depression scale score, mean ± SD (range 0–33)	3.7 ± 3.9	5.3 ± 4.8	4.7 ± 4.8)	4.1 ± 4.2

SD = standard deviation.

were 2.7 (95% CI = 1.45–4.98) and 3.5 (95% CI = 1.92–6.28), respectively, for subjects who reported subjective memory deterioration at baseline and who reported new subjective memory deterioration at follow-up, after adjusting for baseline performance on CASI and STM, baseline CES-D scores, age of reporting subjective memory deterioration, ApoE genotype, and family history of AD.

Subjective memory deterioration at baseline was associated with incident dementia during follow-up, as illustrated in Figure 1. Of 1,739 participants who had at least 1 year of follow-up, 126 developed dementia, and 1,613 were censored as no dementia at the last follow-up. Age modified the association between subjective memory deterioration and incident dementia, as indicated by the statistically significant interaction between subjective memory deterioration and age at baseline in the Cox model. For example, for persons reporting subjective memory deterioration at the ages of 70, 75, and 80, the HRs of developing dementia were 6.0 (95% CI = 2.1–18), 3.2 (95% CI = 1.6–6.2), and 1.6 (95% CI = 0.86–3.1), respectively. These HRs were adjusted for age, ApoE genotype, family history of AD, and baseline STM and CES-D scores. The baseline CASI score was no longer a significant predictor for incident dementia after including the baseline STM score in the Cox model. No subject entering the study at the age of 65 developed dementia during the study period.

Table 2. Baseline Characteristics by Levels of Subjective Memory Deterioration

Baseline Characteristic	Subjective Memory Rating Scale Score: 15* (n = 536; 28%)	16–19† (n = 1,260; 67%)	20‡ (n = 87; 5%)	Total (N = 1,883; 100%)
Age, mean ± SD	73.6 ± 5.5	74.9 ± 5.9	76.1 ± 6.0	74.6 ± 5.8
Sex, n (%)				
Male	217 (29)	494 (65)	48 (6)	759
Female	319 (28)	766 (68)	39 (3)	1,124
Ethnicity, n (%)				
White	503 (28)	1,195 (67)	74 (4)	1,772
Nonwhite	33 (30)	64 (58)	13 (12)	110
Apolipoprotein E alleles, n (%)				
e3/3	306 (29)	694 (66)	53 (5)	1,053
e2/4	4 (12)	25 (74)	5 (15)	34
e2/2 or e2/3	63 (26)	167 (68)	15 (6)	245
e3/4 or e4/4	104 (27)	265 (70)	12 (3)	381
Missing	59 (35)	109 (64)	2 (1)	170
Family history of Alzheimer's disease, n (%)				
No	502 (28)	1,183 (67)	79 (5)	1,764
Yes	34 (29)	77 (65)	8 (7)	119
Short-term memory recall score (0–12)				
≤9, n (%)	41 (19)	164 (77)	9 (4)	214
10–12, n (%)	495 (30)	1,096 (66)	78 (5)	1,669
Mean ± SD	11.1 ± 1.1	10.9 ± 1.2	10.95 ± 1.0	11.0 ± 1.2
Cognitive ability screening instrument score (0–100)				
91–93, n (%)	117 (23)	378 (73)	25 (5)	520
94–97, n (%)	311 (31)	632 (64)	45 (5)	988
98–100, n (%)	108 (29)	250 (67)	17 (5)	375
Mean ± SD	95.4 ± 2.3	95.1 ± 2.4	95.1 ± 2.4	95.2 ± 2.4
Education, years				
<12, n (%)	51 (31)	101 (62)	10 (6)	162
≥12, n (%)	485 (28)	1,156 (68)	77 (4)	1,718
Mean ± SD	14.3 ± 2.7	14.2 ± 2.7	14.6 ± 3.1	14.2 ± 2.7
Depression				
Center for Epidemiologic Studies Depression scale score, mean ± SD (range 0–33)	3.0 ± 3.4	4.3 ± 4.4	6.2 ± 5.0	4.1 ± 4.2

*No self-perceived deterioration.
†Some deterioration.
‡Definite deterioration.
SD = standard deviation.

To assess the potential biases that subjects who died or were lost to follow-up might introduce, logistic regression was performed to examine whether subjective memory deterioration was associated with death and dropout. It was found that subjective memory deterioration at baseline was not associated with death and dropout. Therefore, the influence of death and dropout on the estimates for the associations of subjective memory deterioration with cognitive decline and incident dementia was minimal in this study.

DISCUSSION

It was found that older people with subjective memory deterioration at baseline were at greater risk of developing dementia during 5 years of follow up, even though at baseline they performed as well as those without subjective memory deterioration on the CASI and the short-term memory recall. These findings support the hypothesis that subjective memory deterioration provides additional information about future dementia at a time when a screening test does not show objective evidence of cognitive impairment. A screening test administered at one point measures levels of cognitive function but not the change in cognitive function of a person over time. In contrast, subjective memory deterioration assesses self-perceived change over time in a person, but longitudinal assessments including better measures of subjective memory deterioration and objective memory function are necessary to determine the validity of self-reported memory changes over time. Nevertheless, it is reasonable to speculate that high-performing individuals may be aware of decline in their memory, when

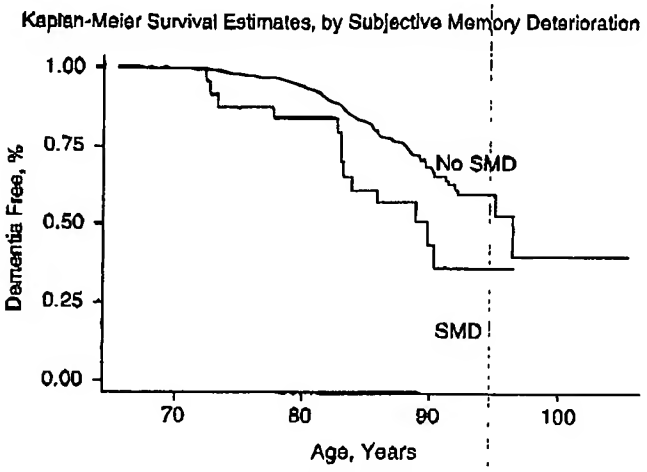

Figure 1. Kaplan-Meier survival estimates for the probabilities of being dementia free. Subjects who reported subjective memory deterioration (SMD) but scored normal on the Cognitive Ability Screening Instrument at baseline were less likely to be dementia free than those who reported no SMD.

they are still able to perform in the normal range on a screening test. Subjective memory deterioration might indicate mild cognitive impairments that could be detected if a more comprehensive assessment were used.

One of the strengths of this study is its prospective, longitudinal nature. This design avoids some of the pitfalls inherent in cross-sectional measurement of longitudinally developing processes.[23] The principal findings of this study are that a high level of subjective memory deterioration was associated with cognitive decline and future dementia in older people who did not have objective cognitive impairment according to a screening test; age modified the association between subjective memory deterioration and future dementia, with younger persons reporting subjective memory deterioration having a higher risk of dementia than older persons reporting subjective memory deterioration. One report from the ASE found that, for 2,169 subjects with normal baseline cognition, memory complaints were associated with incident AD in 3 years of follow-up.[7] Another ASE report found that memory complaints were associated with accelerated cognitive decline over 6 years of follow-up in cognitively normal elderly.[9] These two studies used a single question to assess subjective memory: "Do you have complaints about your memory?" A smaller longitudinal study with 331 subjects (20 subjects with dementia) and 7 to 8 years follow-up showed that memory complaints reflected perceptions of past memory performance and an early manifestation of memory impairment.[5] The association between complaints and future memory performance was present even when dementia cases were excluded, but the magnitude of the association decreased. In this study,[5] memory complaints were assessed using four specific questions regarding whether a person's memory had become worse ((1) remembering recent things, (2) remembering where belongings were located, (3) recalling conversations, and (4) remembering appointments and social arrangements) and compared with earlier in life. Although the differences in subjective memory measures and study methods make results difficult to compare across the studies, the results of the current study are consistent with these longitudinal studies[5,7,9] and provide evidence that subjective memory deterioration can be associated with subsequent cognitive decline and future dementia.

Subjective memory deterioration was associated with a higher risk of developing dementia in younger persons than in older persons. Although these analyses showed that the magnitude of this effect modification by age was large, the finding needs to be confirmed and replicated in other studies. It is possible that small numbers of persons with subjective memory deterioration who developed dementia in various age groups may generate an unstable estimate for the interaction of subjective memory deterioration with age. If these findings are confirmed, there are several possible explanations for this effect modification. One possibility is that younger old persons may assess their memory changes more correctly than older persons. Because executive impairments develop with age, self-assessment of subjective memory may become less reliable in older age. Another possible explanation is that memory problems are more common in older age groups (≥ 80), so it is more difficult to distinguish whether subjective memory deterioration is an early sign of dementia or so-called normal aging. This is probably related to the fact that cognitive function changes, like so many age-related changes, have increased variance with age and increased frequency with age; thus, the distinction between normal and abnormal becomes more difficult at older ages.

The data showed that subjective memory deterioration at baseline and new subjective memory deterioration at follow-up were strongly associated with decline in cognitive performance. The subjective memory deterioration measure has adequate face validity, but the subjective memory deterioration scale was imprecise and had a low predictive value for dementia, which implies that, in its present form, it would likely have limited clinical utility. This measure is not proposed as a diagnostic test for detecting early dementia. Better measurement of subjective memory may help improve the ability to identify a subgroup of individuals at high risk for developing dementia. The need for instrument development in assessing changes in subjective memory, which combined with clinical tests, might have potential to be a practical way of identifying individuals in an early stage of developing dementia, is stressed. Of the five memory items, the judgment of time reflects orientation rather than memory. Thus, subjective memory deterioration as defined in this study might assess a broader range of cognitive decline than memory per se.

The relationship between subjective memory complaints and depression has been reported.[24,25] It was found in the current study that subjective memory deterioration at baseline was associated with higher CES-D scores. After adjusting for CES-D score, there was still a significant relationship between baseline subjective memory deterioration and incident dementia, but because extensive psychometric measurements were not performed on persons who were in the normal range on the screening test, it cannot be ascertained whether subjective memory deterioration was due to subtle but real impairments or to some other causes like depression.

Studies have reported that education levels were associated with memory complaints[2,15] and cognitive decline

and dementia,[26–28] although other studies had different results.[29,30] It was found that education levels were not associated with subjective memory deterioration at baseline or incident dementia at follow-up in this well-educated cohort. The analyses might have been underpowered to detect such associations if they exist, because there were few subjects with low levels of education (2% with ≤8 years and 6% with 9–11 years of education). These findings may apply only to relatively well-educated populations.

It may be important to identify individuals at high risk of developing AD and other types of dementia at an early stage. When effective interventions become available, early treatment may slow the development of disease and prevent further irreversible damage from occurring. The current study suggests that some older individuals with normal cognitive functioning who go on to develop dementia appear to be able to discern changes in their memory before those changes are apparent on cognitive screening tests. This study adds to the growing body of evidence that suggests that a high level of subjective memory deterioration may represent an early sign of dementia in a subset of individuals. Present research tools are too blunt to apply widely, and future work should develop better tools to measure this area.

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Treating Mild Cognitive Impairment

The Absence of Evidence

E. S. Roach, MD

The absence of evidence does not constitute evidence of absence.
William Safire

Most people with Alzheimer disease (AD) develop mild cognitive impairment (MCI) as an initial step toward progressively severe dementia, but there are numerous other causes of MCI. If we define AD by its pathological changes rather than by the severity and variety of its signs and symptoms, then many, perhaps even most, individuals with MCI will eventually prove to have early AD. And if a medication improves cognitive function of a person with AD, even modestly, why not treat individuals with MCI? It seems reasonable to guess that a medication known to alleviate symptoms of AD could also be useful in the different conditions with overlapping clinical manifestations.

Scientific disagreements often arise because key facts are missing, and there are many questions we need to answer more completely in order to know how to best deal with MCI. How effective are acetylcholinesterase inhibitors in individuals with MCI? If these drugs improve function in 1 MCI subgroup, can we assume that they will have the same effect in individuals in other subgroups? If a medication is effective, does its use make enough difference to justify the effort, cost, and risks of treatment? If a medication meaningfully improves quality of life, can we justify not using it?

Gauthier and Touchon[1] argue that although individuals with MCI have an increased likelihood of progressing to frank dementia during a 10-year interval, many of them remain stable and some even revert to normal during this period. Moreover, the heterogeneity and unpredictability of MCI make it difficult to treat affected individuals with cholinesterase inhibitors. Randomized clinical trials using these drugs in people with MCI have not demonstrated consistent improvement in cognition or lowered the likelihood of developing AD after MCI.[1]

While Petersen and Morris[2] agree that MCI is heterogeneous, they argue that much of this variability is likely to disappear as we become more precise in defining MCI subtypes and identifying its different causes. More accurate classification, in turn, creates an opportunity to offer treatment to selected individuals before their symptoms become advanced.[2] Both sides agree on the need for continuing studies.

Reasonable arguments can be made both for and against treating individuals with MCI with cholinesterase inhibitors. Mild cognitive impairment is not a unique clinical entity, and proof that the available drugs benefit conditions other than AD is lacking. Nevertheless, many individuals with MCI progress to AD, and it seems intuitive that earlier treatment should be more effective. This debate should not obscure the fact that the currently available drugs are not dramatically effective even under ideal circumstances, and we must continue our efforts to develop other types of therapy for MCI and AD.

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Submissions

We invite you to suggest controversies and 3 names of potential authors to write about either side of the issue. Do not feel that you need to exclude yourself. Please communicate with E. S. Roach, MD, Department of Neurology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157; phone (336) 716-1619; fax (336) 716-9489 (sroach@wfubmc.edu).

Mild Cognitive Impairment Is Not a Clinical Entity and Should Not Be Treated

Serge Gauthier, MD, FRCPC; Jacques Touchon, MD

THERE HAS BEEN GREAT progress in the diagnosis and treatment of Alzheimer disease (AD) and related dementias thanks to the availability of well-validated diagnostic criteria (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), National Institute of Neurological and Communicative Disorders and Stroke–the Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA]); and a large number of randomized clinical trials using cholinesterase inhibitors (AChEIs) and Memantine. Work from specialized neurological clinics suggests that mild cognitive impairment (MCI) is an early stage of AD, and there is a temptation for neurologists to prescribe AChEIs in this population. On the other hand, there is epidemiological evidence that many subjects labeled as having MCI do not worsen over time and may revert to normal cognitive abilities. A diagnosis of MCI as a predementia stage of AD in such individuals would be inaccurate and carry a heavy personal and societal burden. Reversible causes of MCI may be found, such as depression, upper airway obstruction, and a variety of metabolic, nutritional, or sensory impairments. Since MCI does not constitute a homogeneous clinical syndrome, it is inappropriate to propose a specific drug treatment such as AChEIs, but the recognition that MCI is a risk state toward further cognitive decline is clinically relevant, and control of risk factors such as systolic hypertension, hypercholesterolemia, diabetes mellitus, atrial fibrillation, transient ischemic attacks, and strokes may delay progression to dementia.

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GENERAL CONCEPT OF MCI

The concept of MCI is being widely used in epidemiological and clinical studies as an intermediate stage between cognitive normality and dementia. A high number of persons have been found to have MCI in the population at large, and many are now being referred to memory clinics. There is an expectation that even larger numbers of individuals with memory complaints will be coming forward for assessment in the near future.

The heterogeneity of MCI has been recognized in a report of the Quality Standards Subcommittee of the American Academy of Neurology,[1] where it has been recommended to qualify the term *MCI* with an appropriate modifier such as "amnestic," which was defined operationally by Petersen et al[2] in 1999 (**Figure 1**).

- Subjective memory complaint, preferably corroborated by an informant
- Memory impairment relative to age-matched and education-matched healthy individuals
- Relatively normal general cognitive function
- Largely intact activities of daily living
- Not demented

Figure 1. Operational definition of amnestic mild cognitive impairment.

MCI IN SPECIALTY CLINICS

Specialized clinics in Rochester, Minn, and St Louis, Mo, have established that amnestic MCI is frequently a prodrome to AD[2] or its first manifestation.[3] Conversion rates from amnestic MCI to AD range from 12% to 15% per year.[3] The heterogeneity within MCI has been noted and a new classification has been proposed, based predominantly on neuropsychological profiles, and includes amnestic or single memory MCI, multiple-domain MCI, and single nonmemory MCI.[4]

MCI IN POPULATION STUDIES

Estimates of prevalence of MCI in population-based epidemiological studies vary greatly depending on the definition in use and range from 3% to 16.0%.[5] The former figure is obtained from specialized referral clinics using amnestic MCI criteria, whereas the latter figure has been documented in the Canadian Study of Health and Aging where the term *cognitive impairment no dementia* (CIND) was defined as various categories of impairment identified in a clinical examination and neuropsychological tests.[6] The most common cause of CIND was circumscribed memory impairment, a close equivalent to amnestic MCI, with a prevalence of 5.3%.[7] The follow-up of individuals from that cohort with MCI defined by different criteria led to a wide range of conversion to dementia (20.0%-50.9%), AD (11.6%-28.8%), and death (30.1%-42.4%).[8]

An epidemiological study based on a general practice research network in France revealed a prevalence of 3.2% for MCI, which was a poor predictor of dementia within a 3-year period, with an 11.1% conversion rate and many subjects reverting to normal cognition.[9] Another cohort in France demonstrated a prevalence of 2.8% for MCI and an annual conversion rate of 8.3% across 3 years, but within 3 years more than 40% of subjects with MCI had reverted to normal cognition.[10]

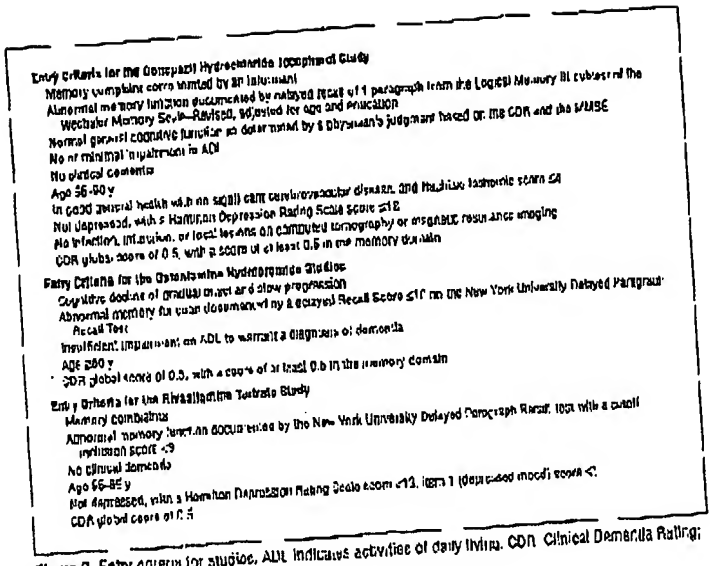

Figure 2. Entry criteria for studies. ADL indicates activities of daily living; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.

The Kungsholmen Project is another population study looking at MCI, where a distinction was made within CIND as mild, moderate, or severe based on Mini Mental State Examination scores (mild, 1 SD lower than age-specific mean scores; moderate, 1.5 SDs; severe, 2 SDs). Depression and cerebrovascular disease were more common in the CIND population compared with unimpaired subjects; similar proportions of subjects with CIND progressed to dementia, death, and cognitive improvement across 3 years.[11]

A community-based sample in a rural area of the United States showed that 3% to 4% of elderly persons without dementia met MCI criteria and had a higher risk of progressing to dementia across 10 years, but many remained stable or reverted to normal cognition during follow-up.[12]

MCI IN RANDOMIZED CLINICAL TRIALS

The operational definition of amnestic MCI has made possible large-scale, placebo-controlled, randomized clinical trials to test the hypothesis that the treatment of MCI with AChEIs, such as donepezil hydrochloride, rivastigmine tartrate, or galantamine hydrobromide, can delay the diagnosis of AD and/or improve cognitive impairments. Different MCI populations are defined for each study[13-15] (**Figure 2**).

Results of these studies are only partially analyzed and reported, but for the purpose of the arguments in the "Controversies" section, there was a wide range of rate of conversion to AD across 2 to 4 years. This variability is based on differences in the number of carriers of the apolipoprotein E4 genotype, variations in the memory impairment cutoff scores at entry, and the heterogeneity of MCI, even in the relatively pure amnestic subtype. Efficacy of AChEIs overall in improving cognition or delaying the conversion from MCI to AD have been disappointing so far.

MCI AT HIGHER RISK OF CONVERSION TO DEMENTIA

There are patterns emerging from specialized neurological clinics, population studies, and randomized clinical trials for higher risks of progression to dementia. It is likely that models combining multiple risk factors, such as the ones listed in **Figure 3**,[9,10,12] will be needed for predicting the risk of individuals with MCI for progression to dementia.

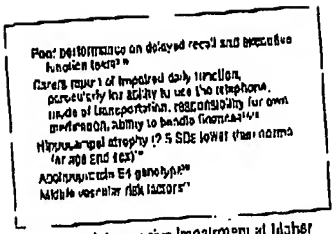

Figure 3. Mild cognitive impairment at higher risk of progression to dementia.

MCI IN CLINICAL PRACTICE

A classification of MCI has been proposed for use in clinical practice based on the main subtypes of patients older than 70 years commonly encountered in neurology referral practice[16]: dysphoric, vascular, amnestic, miscellaneous, or other medical conditions. The importance of neuropsychiatric symptoms in MCI is starting to emerge from systematic studies using the Neuropsychiatric Inventory, with depression, apathy, and irritability being most common.[17] We think that this is the most common type of MCI, which we label as "dysphoric." The second most common is "vascular" (eg, individuals with cognitive impairment associated with vascular risk factors and vascular lesions on computed tomography and/or magnetic resonance imaging). Less common is amnestic as defined earlier. A "miscellaneous" category could include other causes, such as sleep apnea, alcohol abuse, metabolic and nutritional deficiencies, sensory deprivation, and head injury.

Since the depressive or dysphoric MCI profile may represent a noncognitive prodrome to dementia[18] or even subclinical AD,[19] yearly follow-up visits are suggested beyond treating depressive symptoms with a serotonin reuptake inhibitor or other relevant drug and supportive psychotherapy. Although less likely to deteriorate over time, vascular MCI requires treatment and follow-up of the associated conditions. Finally, amnestic MCI requires follow-up until dementia is diagnosable, at which time an AChEI should be offered. Miscellaneous causes of MCI are reversible for the most part with treatment of the specific etiologies, often coexisting.

Subject and/or informant reports cognitive problems
These represent a decline relative to the subject's previous abilities
Demonstration of mild cognitive impairment by cognitive testing, in memory, and/or other domains
This cognitive impairment does not cause functional impairment in daily life
Absence of dementia based on clinical judgment

Figure 4. Syndromic definition of mild cognitive impairment.

FUTURE PERSPECTIVE ON MCI

A future perspective on dealing with MCI would be (1) defining MCI as a clinical syndrome with diagnostic criteria, (2) defining clinical subtypes of MCI, and (3) defining etiological subtypes of MCI and then treating accordingly.

For the first step, a set of clinical criteria based on a clinical approach may be preferred to a predominantly neuropsychological one. These criteria could be created and used in a way similar to *DSM IV* or NINCDS-ADRDA criteria. As a starting point, we have made a proposal for new MCI criteria (**Figure 4**).[21]

A working group of health care professionals and epidemiologists proposed similar criteria for MCI[26] based on 3 diagnostic features: (1) not normal, without dementia, (2) cognitive decline indicated by subject and/or informant report and objective cognitive tests, and (3) preserved basic activities of daily living with some minimal impairment in complex instrumental functions.

The second step in dealing with MCI will be the characterization of the different subtypes, which can be defined using primarily neuropsychological criteria or primarily clinical criteria, and determining their natural history.

The third step will be the characterization of the etiology of each clinical subtype and its specific treatments. It is possible that amnestic MCI will become "very early AD" and be incorporated into updated NINCDS-ADRDA–like criteria.

CONCLUSIONS

Guidelines such as the ones developed by the American Academy of Neurology[1] need to be updated as new evidence on the natural history of amnestic and other types of MCI become available. Until then, we argue that MCI is not a homogeneous clinical entity and, as such, cannot be treated with a specific therapy such as AChEIs. On the other hand, reversible causes of MCI may be found, such as depression, upper airway obstruction, and a variety of metabolic, nutritional, or sensory impairments, whereas control of vascular risk factors such as systolic hypertension, hypercholesterolemia, diabetes mellitus, atrial fibrillation, transient ischemic attacks, and strokes may delay progression to dementia.

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Author Contributions: *Study concept and design:* Gauthier and Touchon. *Drafting of the manuscript:* Gauthier and Touchon. *Administrative, technical, and material support:* Gauthier and Touchon.

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Nizoral—Cont.

In rare cases anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported.

Coadministration of ketoconazole tablets and terfenadine has led to elevated plasma concentrations of terfenadine which may prolong QT intervals, sometimes resulting in life-threatening cardiac dysrhythmias. Cases of torsades de pointes and other serious ventricular dysrhythmias, in rare cases leading to fatality, have been reported among patients taking terfenadine concurrently with ketoconazole tablets. Coadministration of ketoconazole tablets and terfenadine is contraindicated.

Coadministration of astemizole with ketoconazole tablets is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS sections.)

Concomitant administration of NIZORAL® Tablets with cisapride is contraindicated because it has resulted in markedly elevated cisapride plasma concentrations and prolonged QT interval, and has rarely been associated with ventricular arrhythmias and torsades de pointes. (See BOX WARNINGS, CONTRAINDICATIONS and PRECAUTIONS sections.)

In European clinical trials involving 350 patients with metastatic prostatic cancer, eleven deaths were reported within two weeks of starting treatment with high doses of ketoconazole tablets (1200 mg/day). It is not possible to ascertain from the information available whether death was related to ketoconazole therapy in these patients with serious underlying disease. However, high doses of ketoconazole tablets are known to suppress adrenal corticosteroid secretion.

In female rats treated three to six months with ketoconazole at dose levels of 80 mg/kg and higher, increased fragility of long bones, in some cases leading to fracture, was seen. The maximum "no-effect" dose level in these studies was 20 mg/kg (2.5 times the maximum recommended human dose). The mechanism responsible for this phenomenon is obscure. Limited studies in dogs failed to demonstrate such an effect on the metacarpals and ribs.

PRECAUTIONS

General: NIZORAL® (ketoconazole) Tablets have been demonstrated to lower serum testosterone. Once therapy with NIZORAL® Tablets has been discontinued, serum testosterone levels return to baseline values. Testosterone levels are impaired with doses of 800 mg per day and abolished by 1600 mg per day. NIZORAL® Tablets also decrease ACTH induced corticosteroid serum levels at similar high doses. The recommended dose of 200 mg–400 mg daily should be followed closely.

In four subjects with drug-induced achlorhydria, a marked reduction in ketoconazole absorption was observed. NIZORAL® Tablets require acidity for dissolution. If concomitant antacids, anticholinergics, and H_2-blockers are needed, they should be given at least two hours after administration of NIZORAL® Tablets. In cases of achlorhydria, the patients should be instructed to dissolve each tablet in 4 mL aqueous solution of 0.2 N HCl. For ingesting the resulting mixture, they should use a drinking straw so as to avoid contact with the teeth. This administration should be followed with a cup of tap water.

Information for Patients: Patients should be instructed to report any signs and symptoms which may suggest liver dysfunction so that appropriate biochemical testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stools (see WARNINGS section).

Drug Interactions: Ketoconazole is a potent inhibitor of the cytochrome P450 3A4 enzyme system. Coadministration of NIZORAL® Tablets and drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse effects. Therefore, unless otherwise specified, appropriate dosage adjustments may be necessary. The following drug interactions have been identified involving NIZORAL® Tablets and other drugs metabolized by the cytochrome P450 3A4 enzyme system.

Ketoconazole tablets inhibit the metabolism of terfenadine, resulting in an increased plasma concentration of terfenadine and a delay in the elimination of its acid metabolite. The increased plasma concentration of terfenadine or its metabolite may result in prolonged QT intervals. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS sections.)

Human pharmacokinetics data indicate that oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. Therefore concomitant administration of ketoconazole tablets with cisapride is contraindicated. (See BOX WARNINGS, CONTRAINDICATIONS, and WARNINGS sections.)

Ketoconazole tablets may alter the metabolism of cyclosporine, tacrolimus, and methylprednisolone, resulting in elevated plasma concentrations of the latter drugs. Dosage adjustment may be required if cyclosporine, tacrolimus, or methylprednisolone are given concomitantly with NIZORAL® Tablets.

Coadministration of NIZORAL® Tablets with midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. These agents should not be used in patients treated with NIZORAL® Tablets. If midazolam is administered parenterally, special precaution is required since the sedative effect may be prolonged.

Rare cases of elevated plasma concentrations of digoxin have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor digoxin concentrations in patients receiving ketoconazole.

When taken orally, imidazole compounds like ketoconazole may enhance the anticoagulant effect of coumarin-like drugs. In simultaneous treatment with imidazole drugs and coumarin drugs, the anticoagulant effect should be carefully titrated and monitored.

Because severe hypoglycemia has been reported in patients concomitantly receiving oral miconazole (an imidazole) and oral hypoglycemic agents, such a potential interaction involving the latter agents when used concomitantly with ketoconazole tablets (an imidazole) cannot be ruled out.

Concomitant administration of ketoconazole tablets with phenytoin may alter the metabolism of one or both of the drugs. It is suggested to monitor both ketoconazole and phenytoin.

Concomitant administration of rifampin with ketoconazole tablets reduces the blood levels of the latter. INH (Isoniazid) is also reported to affect ketoconazole concentrations adversely. These drugs should not be given concomitantly.

After the coadministration of 200 mg oral ketoconazole twice daily and one 20 mg dose of loratadine to 11 subjects, the AUC and C_{max} of loratadine averaged 302% (± 142 S.D.) and 251% (± 68 S.D.), respectively, of those obtained after co-treatment with placebo. The AUC and C_{max} of descarboethoxyloratadine, an active metabolite, averaged 155% (± 27 S.D.) and 141% (± 35 S.D.), respectively. However, no related changes were noted in the QT_c on ECG taken at 2, 6, and 24 hours after the coadministration. Also, there were no clinically significant differences in adverse events when loratadine was administered with or without ketoconazole.

Rare cases of a disulfiram-like reaction to alcohol have been reported. These experiences have been characterized by flushing, rash, peripheral edema, nausea, and headache. Symptoms resolved within a few hours.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames Salmonella microsomal activator assay was also negative. A long term feeding study in Swiss Albino mice and in Wistar rats showed no evidence of oncogenic activity.

Pregnancy: Teratogenic effects: Pregnancy Category C: Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given in the diet at 80 mg/kg/day (10 times the maximum recommended human dose). However, these effects may be related to maternal toxicity, evidence of which also was seen at this and higher dose levels.

There are no adequate and well controlled studies in pregnant women. NIZORAL® Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Ketoconazole has also been found to be embryotoxic in the rat when given in the diet at doses higher than 80 mg/kg during the first trimester of gestation. In addition, dystocia (difficult labor) was noted in rats administered oral ketoconazole during the third trimester of gestation. This occurred when ketoconazole was administered at doses higher than 10 mg/kg (higher than 1.25 times the maximum human dose).

It is likely that both the malformations and the embryotoxicity resulting from the administration of oral ketoconazole during gestation are a reflection of the particular sensitivity of the female rat to this drug. For example, the oral LD_{50} of ketoconazole given by gavage to the female rat is 166 mg/kg whereas in the male rat the oral LD_{50} is 287 mg/kg.

Nursing Mothers: Since ketoconazole is probably excreted in the milk, mothers who are under treatment should not breast feed.

Pediatric Use: NIZORAL® (ketoconazole) Tablets have not been systematically studied in children of any age, and essentially no information is available on children under 2 years. NIZORAL® Tablets should not be used in pediatric patients unless the potential benefit outweighs the risks.

ADVERSE REACTIONS

In rare cases, anaphylaxis has been reported after the first dose. Several cases of hypersensitivity reactions including urticaria have also been reported. However, the most frequent adverse reactions were nausea and/or vomiting in approximately 3%, abdominal pain in 1.2%, pruritus in 1.5%, and the following in less than 1% of the patients: headache, dizziness, somnolence, fever and chills, photophobia, diarrhea, gynecomastia, impotence, thrombocytopenia, leukopenia [illegible]

[illegible] has been reported in investigational [illegible] drug at dosages above those currently [illegible] mia has not been reported at dosages [illegible] however sperm counts have been obtained [illegible] patients treated with these dosages. Most of [illegible] were mild and transient and rarely req[illegible] tion of NIZORAL® (ketoconazole) Tablets [illegible] rare occurrences of hepatic dysfunction [illegible] tection (see WARNINGS section).

In worldwide postmarketing experience [illegible] Tablets there have been rare reports of [illegible] sia, and signs of increased intracranial [illegible] bulging fontanelles and papilledema [illegible] has also been reported but a causal [illegible] NIZORAL® Tablets is uncertain.

Neuropsychiatric disturbances, including [illegible] dies and severe depression, have been [illegible] using NIZORAL® Tablets.

Ventricular dysrhythmias (prolonged [illegible]) occurred with the concomitant use of [illegible] conazole tablets. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS sections.) The [illegible] ministration of ketoconazole tablets [illegible] result in prolongation of the QT interval [illegible] been associated with ventricular arrhythmias [illegible] TRAINDICATIONS, WARNINGS, [illegible] sections.)

OVERDOSAGE

In the event of accidental overdosage, [illegible] including gastric lavage with sodium bic[illegible] employed.

DOSAGE AND ADMINISTRATION

Adults: The recommended starting dose of NIZORAL® (ketoconazole) Tablets is a single daily [illegible] 200 mg (one tablet). In very serious infections [illegible] responsiveness is insufficient within the [illegible] dose of NIZORAL® Tablets may be increased [illegible] tablets) once daily.

Children: In small numbers of children [illegible] a single daily dose of 3.3 to 6.6 mg/[illegible] NIZORAL® Tablets have not been studied [illegible] 2 years of age.

There should be laboratory as well as [illegible] tion of infection prior to starting [illegible] Treatment should be continued until [illegible] tive fungal infection has subsided. [illegible] treatment may yield poor response and [illegible] rence of clinical symptoms. Minimum [illegible] diasis is one or two weeks. Patients [illegible] taneous candidiasis usually require [illegible] Minimum treatment for the other [illegible] sez is six months.

Minimum treatment for recalcitrant [illegible] tions is four weeks in cases involving [illegible] and plantar infections may respond [illegible] cence may subsequently occur after [illegible] apy in some cases.

HOW SUPPLIED

NIZORAL® (ketoconazole) is available [illegible] lets containing 200 mg of [illegible] "JANSSEN" and on the reverse side [illegible] They are supplied in bottles of 100 [illegible] 100.

Store at controlled room temperature [illegible] 15°–25°C (59°–77°F). Protect from [illegible]

U.S. Patent 4,335,125

Rev. March 1997, July 1998

JANSSEN PHARMACEUTICA

Titusville, NJ 08560-0200

Shown in Product Identi[illegible]

REMINYL®

[rĕm-i-nil]

GALANTAMINE HBr

TABLETS AND ORAL SOLUTION

DESCRIPTION

REMINYL® (galantamine hydro[illegible]) competitive acetylcholinesterase [illegible] chemically as (4aS,6R,8aS)-4a[illegible] methoxy-11-methyl-6H-benzofuro[illegible] 6-ol hydrobromide. It has [illegible] $C_{17}H_{21}NO_3 \cdot HBr$ and a molecular [illegible] tamine hydrobromide is a white [illegible] is sparingly soluble in water [illegible] galantamine hydrobromide is [illegible]

REMINYL® for oral use [illegible] film-coated tablets of 4 [illegible] 12 mg (orange-brown) [illegible] [illegible] tablet contains 5.12[illegible]

[illegible], respectively. Inactive ingredients include [illegible] silicon dioxide, crospovidone, hydroxypropyl [illegible] lactose monohydrate, magnesium stearate, [illegible] cellulose, propylene glycol, talc, and titanium [illegible] 4 mg tablets contain yellow ferric oxide. [illegible] contain red ferric oxide. The 12 mg tablets [illegible] oxide and FD&C yellow #6 aluminum [illegible]

[illegible] available as a 4 mg/mL oral solution. [illegible] ingredients for this solution are methyl [illegible] propyl parahydroxybenzoate, sodium [illegible] hydroxide and purified water.

[illegible]ACOLOGY

[illegible] of cognitive impairment in Alzheimer's [illegible] is not fully understood, it has been reported [illegible] choline-producing neurons degenerate in [illegible] with Alzheimer's disease. The degree [illegible] loss has been correlated with degree of [illegible] and density of amyloid plaques (a [illegible] hallmark of Alzheimer's disease).

[illegible] tertiary alkaloid, is a competitive and reversible [illegible] acetylcholinesterase. While the precise [illegible] mechanism of action is unknown, it is postulated [illegible] therapeutic effect by enhancing cholinergic [illegible] accomplished by increasing the concentration [illegible] through reversible inhibition of its hydrolysis [illegible] esterase. If this mechanism is correct, [illegible] may lessen as the disease process advances [illegible] cholinergic neurons remain functionally [illegible] evidence that galantamine alters the [illegible] underlying dementing process.

[illegible] absorbed with absolute oral bioavailability [illegible] It has a terminal elimination half-life [illegible] pharmacokinetics are linear over the [illegible]

[illegible] of anticholinesterase activity of [illegible] about one hour after a single oral [illegible] in healthy male subjects.

[illegible] absorption

[illegible] and completely absorbed with time [illegible] about 1 hour. Bioavailability of the [illegible] the bioavailability of an oral solution [illegible] the AUC of galantamine but C_{max} [illegible] T_{max} was delayed by 1.5 hours. The [illegible] of galantamine is 175 L.

[illegible] binding of galantamine is 18% at therapeutic [illegible] concentrations. In whole blood, galantamine [illegible] to blood cells (52.7%). The [illegible] ratio of galantamine is 1.2.

[illegible] metabolized by hepatic cytochrome P450 [illegible] and excreted unchanged in the [illegible] indicate that cytochrome CYP2D6 [illegible] major cytochrome P450 isoenzymes [illegible] of galantamine, and inhibitors [illegible] oral bioavailability of galantamine [illegible] PRECAUTIONS, Drug-Drug Interactions [illegible] mediated by CYP2D6 was greater [illegible] of CYP2D6 than in poor metabolizers [illegible] poor and extensive metabolizers, [illegible] galantamine and its glucuronide [illegible] sample radioactivity.

[illegible] galantamine, unchanged galantamine [illegible] counted for most plasma radioactivity [illegible] CYP2D6 metabolizers. Up to 8 [illegible] galantamine accounted for 39[illegible] activity in the plasma, and galantamine [illegible] 24%. By 7 days, 93-99% of the [illegible] recovered, with about 95% in urine [illegible] Total urinary recovery of unchanged [illegible] accounted for, on average, 32% of the [illegible] glucuronide for another 12%.

[illegible], about 20% of the dose was [illegible] galantamine in the urine in 24 [illegible] renal clearance of about 65 mL/min, [illegible] plasma clearance of about 300 mL/[illegible]

[illegible] general population has a genetic [illegible] reduced levels of activity of CYP2D6 [illegible] have been referred to as poor metabolizers [illegible] dose of 4 mg or 8 mg galantamine [illegible] showed demonstrated a similar [illegible] increase of unchanged galantamine [illegible] metabolizers.

[illegible] Alzheimer's disease enrolled in [illegible] genotyped with respect to [illegible] extensive metabolizers, 126 homozygous [illegible] poor metabolizers. Population [illegible] indicated that there was a [illegible] in poor metabolizers [illegible]. Dosage adjustment is [illegible] identified as poor metabolizers as [illegible] titrated to tolerability.

[illegible] a single 4 mg dose of galantamine [illegible] of galantamine in subjects [illegible] (Child-Pugh score of [illegible] healthy subjects. In patients [illegible]

of 7-9), galantamine clearance was decreased by about 25% compared to normal volunteers. Exposure would be expected to increase further with increasing degree of hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment: Following a single 8 mg dose of galantamine, AUC increased by 37% and 67% in moderate and severely renal-impaired patients compared to normal volunteers (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Elderly: Data from clinical trials in patients with Alzheimer's disease indicate that galantamine concentrations are 30-40% higher than in healthy young subjects.

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of REMINYL® (galantamine hydrobromide), but a population pharmacokinetic analysis indicates (n= 539 males and 550 females) that galantamine clearance is about 20% lower in females than in males (explained by lower body weight in females) and race (n=1029 White, 24 Black, 13 Asian and 23 other) did not affect the clearance of REMINYL®.

Drug-Drug Interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on in vitro studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. Galantamine is also glucuronidated and excreted unchanged in urine.

(A) Effect of other drugs on the metabolism of REMINYL®: Drugs that are potent inhibitors for CYP2D6 or CYP3A4 may increase the AUC of galantamine. Multiple dose pharmacokinetic studies demonstrated that the AUC of galantamine increased 30% and 40%, respectively, during coadministration of ketoconazole and paroxetine. As coadministered with erythromycin, another CYP3A4 inhibitor, the galantamine AUC increased only 10%. Population PK analysis with a database of 852 patients with Alzheimer's disease showed that the clearance of galantamine was decreased about 25-33% by concurrent administration of amitriptyline (n=17), fluoxetine (n=48), fluvoxamine (n=14), and quinidine (n=7), known inhibitors of CYP2D6.

Concurrent administration of H_2-antagonists demonstrated that ranitidine did not affect the pharmacokinetics of galantamine, and cimetidine increased the galantamine AUC by approximately 16%.

(B) Effect of REMINYL® on the metabolism of other drugs: In vitro studies show that galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 and CYP2E1. This indicated that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. Multiple doses of galantamine (24 mg/day) had no effect on the pharmacokinetics of digoxin and warfarin (R- and S-forms). Galantamine had no effect on the increased prothrombin time induced by warfarin.

CLINICAL TRIALS

The effectiveness of REMINYL® (galantamine hydrobromide) as a treatment for Alzheimer's disease is demonstrated by the results of 4 randomized, double-blind, placebo-controlled clinical investigations in patients with probable Alzheimer's disease [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores that were ≥10 and ≤24]. Doses studied were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned. In the fourth study (USA 4-week Dose-Escalation Fixed-Dose Study) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in the 4 REMINYL® trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

Study Outcome Measures: In each study, the primary effectiveness of REMINYL® was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus).

The ability of REMINYL® to improve cognitive performance was assessed with the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen [illegible] the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in REMINYL® trials was approximately 4.5 units per year.

The ability of REMINYL® to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and can not be compared directly with the results of CIBIC-plus evaluations from other clinical trials. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioral and activities of daily living. It represents the assessment of a skilled clinician based on his/her observation at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

U.S. Twenty-One-Week Fixed-Dose Study

In a study of 21 weeks duration, 978 patients were randomized to doses of 8, 16, or 24 mg of REMINYL® per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to REMINYL®, and increased by 8 mg/day every 4 weeks. Therefore, the maximum titration phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of REMINYL®).

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL® treated patients compared to the patients on placebo were 1.7, 3.3, and 3.6 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 21 Weeks (5 Months) of Treatment

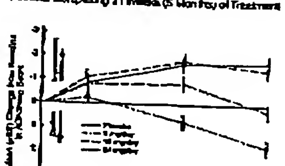

Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL® groups are more likely to show the greater improvements.

[See figure 2 at top of next column]

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups who completed 21 weeks of treatment. The REMINYL®-placebo differences for these groups of patients in mean rating were 0.15, 0.41 and 0.44 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.26 and 0.29, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

[See figure 3 at top of next column]

U.S. Twenty-Six-Week Fixed-Dose Study

In a study of 26 weeks duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL® per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

...ber the metabolism of cyclospor... ...(terfenadine), resulting in ele... ...s of the latter drugs. Dosage ad... ...if cyclosporine, tacrolimus, or ...given concomitantly with ...

...AL® Tablets with midazolam or ...evated plasma concentrations of ...ay potentiate and prolong hyp... ...specially with repeated dosing or ...ese agents. These agents should ...ted with NIZORAL® Tablets. If ...parenterally, special precaution ...ve effect may be prolonged. ...serum concentrations of digoxin ...t clear whether this was due to ...y. It is, therefore, advisable to ...tions in patients receiving keto...

...ole compounds like ketoconazole ...gulant effect of coumarin-like ...atment with imidazole drugs and ...agulant effect should be carefully ...

...ole has been reported to patients ...al miconazole (no imidazole) and ...such a potential interaction in... ...then used concomitantly with ke... ...(azole) cannot be ruled out. ...ine of ketoconazole tablets with ...metabolism of one or both of the ...monitor both ketoconazole and ...

...on of rifampin with ketoconazole ...evels of the latter. INH (Isoniazid) ...ketoconazole concentrations ad... ...ld not be given concomitantly. ...on of 200 mg oral ketoconazole ...dose of loratadine to 11 subjects, ...after averaged 302% (± 142 S.D.) ...spectively, of those obtained after ...e. The AUC and C_{max} of descar... ...tive metabolite, averaged 155% (± ... S.D.), respectively. However, no ...d in the QT, an ECG taken at 2, 6, ...administration. Also, there were no ...ences in adverse events when lor... ...with or without ketoconazole. ...-like reaction to alcohol have been ...ces have been characterized by ...d edema, nausea, and headache. ...n a few hours. ...sis, Impairment of Fertility: The ...t test in male and female mice re... ...doses of ketoconazole as high as ...otation in any stage of germ cell ...Salmonella microsomal activator ...A long term feeding study in Swiss ...y rats showed no evidence of onco...

...c effects: Pregnancy Category ...n shown to be teratogenic (syndac... ...the rat when given in the diet at ...be maximum recommended human ...fects may be related to maternal ...h also was seen at this and higher ...

...nd well controlled studies in preg... ...® Tablets should be used during ...ential benefit justifies the potential ...

...ketoconazole has also been found ...rat when given in the diet at doses ...ring the first trimester of gestation. ...(fault label) was noted in rats ad... ...cole during the third trimester of ...when ketoconazole was administe... ...to 10 mg/kg (higher than 1.25 times ...al.

...malformations and the embryotox... ...ministration of oral ketoconazole ...tion of the particular sensitivity ...For example, the oral LD_{50} of ...the female rat is 166 mg/kg ...LD_{50} is 287 mg/kg. ...azole is probably excreted ...treatment should not ...

...azole) Tablets have not ...of any age, and es... ...children under 2 ...used in pediatric ...weighs the risks.

...after the first ...including ...most fre... ...ing in ap... ...in 1.5%, ...ndache, ...diar... ...dys... ...ash...

...nia has been reported in investigational ...drug at dosages above those currently ap... ...nia has not been reported at dosages up ... however sperm counts have been obtained ...patients treated with these dosages. Most ...were mild and transient and rarely ... ...tion of NIZORAL® (ketoconazole) Tablets ...rare occurrences of hepatic dysfunction ...tection (see WARNINGS section).

In worldwide postmarketing experience ... Tablets there have been rare reports of ...ria, and signs of increased intracranial ...bulging fontanelles and papilledema. ...has also been reported but a causal ... NIZORAL® Tablets is uncertain.

Neuropsychiatric disturbances, including ...des and severe depression, have occurred ...using NIZORAL® Tablets.

Ventricular dysrhythmias (prolonged QT ...occurred with the concomitant use of ter... ...conazole tablets. (See BOX WARNING, C... TIONS, and WARNINGS sections.) Data ...ministration of ketoconazole tablets ...result in prolongation of the QT interval ...been associated with ventricular arrhy... ...TRAINDICATIONS, WARNINGS, and ...sections.)

OVERDOSAGE

In the event of accidental overdosage, ...including gastric lavage with sodium bi... ...employed.

DOSAGE AND ADMINISTRATION

Adults: The recommended starting d... (ketoconazole) Tablets is a single daily ...200 mg (one tablet). In very serious inf... ...responsiveness is insufficient within the ...dose of NIZORAL® Tablets may be incr... ...tablets) once daily.

Children: In small numbers of children ...a single daily dose of 3.3 to 6.6 mg/... NIZORAL® Tablets have not been stud... ...2 years of age.

There should be laboratory as well a... ...tion of infection prior to starting ke... Treatment should be continued until a... ...tive fungal infection has subsided. ...treatment may yield poor response a... ...rence of clinical symptoms. Minimum ...diasis is one or two weeks. Patients w... ...neous candidiasis usually require ... Minimum treatment for the other ind... ...sis is six months.

Minimum treatment for recalcitrant ...tions is four weeks in cases involving ...and plantar infections may respond ...cures may subsequently recur after ...apy in some cases.

HOW SUPPLIED

NIZORAL® (ketoconazole) is availab... ...lets containing 200 mg of k... "JANSSEN" and on the reverse sid... They are supplied in bottles of 100 ... 100.

Store at controlled room temperat... 15°–30°C (59°–77°F). Protect from ... U.S. Patent 4,335,125

Rev. March 1997, July 1998

JANSSEN PHARMACEUTICA

Titusville, NJ 08560-0200

Shown in Product Identificati...

REMINYL®

[rem' i-nil]

(GALANTAMINE HBr)

TABLETS AND ORAL SOLUTION

DESCRIPTION

REMINYL® (galantamine hydro... ...competitive acetylcholinesterase... ...chemically as (4aS,6R,8aS)-4a,... ...methoxy-11-methyl-6H-benzofuro... ...6-ol hydrobromide. It has ... $C_{17}H_{21}NO_3 \cdot HBr$ and a molec... ...tamine hydrobromide is a whi... ...is sparingly soluble in water... ...galantamine hydrobromide is ...

REMINYL® for oral use ... ...film-coated tablets of 4 ... 12 mg (orange-brown) ... ...hard) tablets contain ...

...mide, respectively. Inactive ingredients in... ...dioxide, crospovidone, hydroxypropyl ...lactose monohydrate, magnesium stearate, ...cellulose, propylene glycol, talc, and tita... ...The 4 mg tablets contain yellow ferric oxide. ...contain red ferric oxide. The 12 mg tablets ...oxide and FD&C yellow #6 aluminum ...

...is available as a 4 mg/mL oral solution. ...ingredients for this solution are methyl ...parabens, propyl parahydroxybenzoate, sodium ...hydroxide and purified water.

...MACOLOGY

...ism of Action

...etiology of cognitive impairment in Alzhei... ...is not fully understood, it has been re... ...acetylcholine-producing neurons degenerate in ...people with Alzheimer's disease. The degree ...of this loss has been correlated with degree of ...impairment and density of amyloid plaques (a ...hallmark of Alzheimer's disease).

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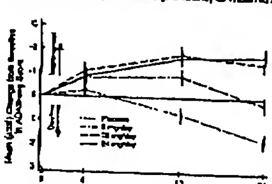
Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 21 Weeks (5 Months) of Treatment



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The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL® groups are more likely to show the greater improvements.

[See figure 2 at top of next column]

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups who completed 21 weeks of treatment. The REMINYL®-placebo differences for these groups of patients in mean rating were 0.15, 0.41 and 0.44 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.26 and 0.29, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

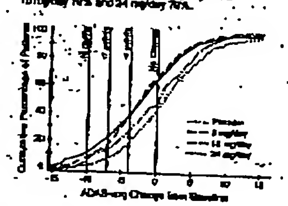
[See figure 3 at top of next column]

U.S. Twenty-Six-Week Fixed-Dose Study

In a study of 26 weeks duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL® per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

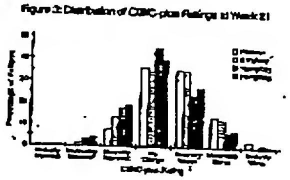
Reminyl—Cont.

Figure 2: Cumulative Percentage of Patients Completing 21 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 8 mg/day 77%, 16 mg/day 78% and 24 mg/day 78%.



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	3.6%	7.6%	19.8%	41.6%
8 mg/day	5.9%	13.9%	21.7%	45.5%
16 mg/day	7.2%	15.9%	35.8%	65.4%
24 mg/day	12.4%	22.7%	37.0%	64.8%

Figure 3: Distribution of CIBIC-plus Ratings at Week 21



Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL®-treated patients compared to the patients on placebo were 3.9 and 3.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 4: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

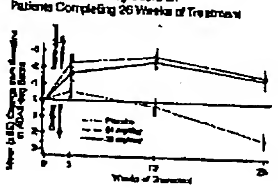


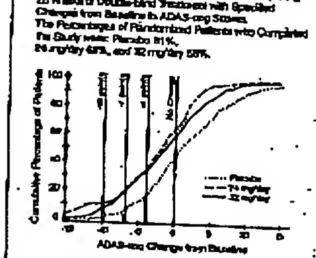
Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to REMINYL® and placebo have a wide range of responses, but that the REMINYL® groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

[See figure 5 at top of next column]

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean REMINYL®-placebo differences for these groups of patients in the mean rating were 0.28 and 0.29 units for 24 and 32 mg/day of REMINYL®, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 81%, 24 mg/day 68%, and 32 mg/day 58%.



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	2.1%	6.7%	18.6%	43.5%
24 mg/day	7.5%	18.3%	33.6%	64.1%
32 mg/day	11.1%	21.7%	33.2%	58.1%

Figure 6: Distribution of CIBIC-plus Ratings at Week 26

International Twenty-Six-Week Fixed-Dose Study

In a study of 26 weeks duration identical in design to the USA 26-Week Fixed-Dose Study, 653 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL® per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose titration phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL®-treated patients compared to the patients on placebo were 3.1 and 4.1 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 7: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

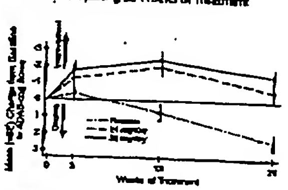


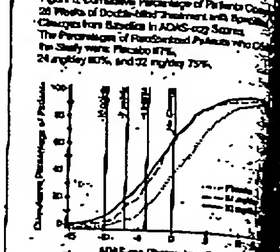
Figure 8 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to REMINYL® and placebo have a wide range of responses, but that the REMINYL® groups are more likely to show the greater improvements.

[See figure 8 at top of next column]

Effects on the CIBIC-plus: Figure 9 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean REMINYL®-placebo differences for these groups of patients in the mean rating of change from baseline were 0.34 and 0.47 for 24 and

Figure 8: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 87%, 24 mg/day 80%, and 32 mg/day 75%.



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	1.2%	3.8%	15.2%	
24 mg/day	4.5%	11.6%	30.8%	
32 mg/day	7.5%	12.7%	24.9%	

for the REMINYL® groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 9: Distribution of CIBIC-plus Ratings at Week 26

International Thirteen-Week Flexible-Dose Study

In a study of 13 weeks duration, 386 patients were randomized to either a flexible dose of 24-32 mg/day of REMINYL® or to placebo, each given in two divided doses. The 13-week study was divided into a 3-week dose titration phase and a 10-week maintenance phase. The patients in the active treatment arm of the study were maintained at either 24 mg/day or 32 mg/day at the discretion of the investigator.

Effects on the ADAS-cog: Figure 10 illustrates the time course for the change from baseline in ADAS-cog scores for both dose groups over the 13 weeks of the study. At 13 weeks of treatment, the mean difference in the ADAS-cog change scores for the treated patients compared to the patients on placebo was 1.9. REMINYL® at a dose of 24-32 mg/day was statistically significantly superior to placebo.

Figure 10: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 13 Weeks of Treatment

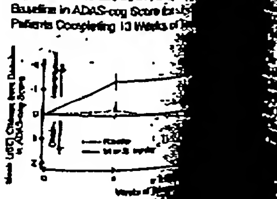


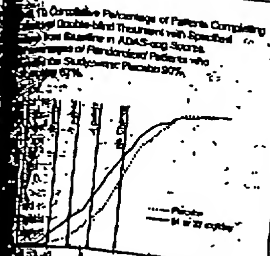
Figure 11 illustrates the cumulative percentages of patients from each of the two treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to REMINYL® and placebo have a wide range of responses, but that the REMINYL® group is more likely to show the greater improvement.

[See figure 11 at top of next column]

Effects on the CIBIC-plus: Figure 12 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the two treatment groups who completed 13 weeks of treatment.

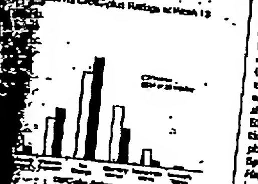
Figure 11: Cumulative Percentage of Patients Completing 13 Weeks of Double-blind Treatment with Specified Changes from Baseline in ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 90%, 24 or 32 mg/day 67%.



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	1.9%	6.0%	19.4%	50.0%
24 or 32 mg/day	3.1%	12.8%	22.2%	65.3%

group was statistically significantly superior to placebo.

Figure 12: Distribution of CIBIC-plus Ratings at Week 13



Patient's age, gender, or race did not predict clinical outcome of treatment.

CONTRAINDICATIONS

REMINYL® (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS

Anesthesia

REMINYL®, as a cholinesterase inhibitor, is likely to exaggerate neuromuscular blocking effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Postmarketing surveillance of marketed cholinesterase inhibitors has shown, however, that bradycardia and all types of heart block have been reported in patients with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction.

In randomized controlled trials, bradycardia was reported more frequently in REMINYL®-treated patients than in placebo-treated patients, but was rarely severe and rarely led to treatment discontinuation. The overall frequency of this event was 2-3% for REMINYL® doses up to 24 mg/day compared with <1% for placebo. No increased incidence of heart block was observed at the recommended doses.

Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo 0.7% [2/286]; 4 mg BID 0.4% [3/692]; 8 mg BID 1.3% [7/552]; 12 mg BID 2.2% [6/273]).

Gastrointestinal Conditions

Through their primary action, cholinomimetics may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g., those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies of REMINYL® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

REMINYL®, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss (see ADVERSE REACTIONS).

Genitourinary

Although this was not observed in clinical trials with REMINYL®, cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions

Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's disease. In clinical trials, there was no increase in the incidence of convulsions with REMINYL® compared to placebo.

Pulmonary Conditions

Because of its cholinomimetic action, galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day, preferably with morning and evening meal) and dose escalation (dose increases should follow minimum of four weeks at prior dose).

Patients and caregivers should be advised that the most frequent adverse events associated with use of the drug can be minimized by following the recommended dosage and administration.

Patients and caregivers should be advised to ensure adequate fluid intake during treatment. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Caregivers should be instructed in the correct procedure for administering REMINYL® (galantamine hydrobromide) Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering REMINYL® Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

Special Populations

Hepatic Impairment

In patients with moderately impaired hepatic function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). The use of REMINYL® in patients with severe hepatic impairment is not recommended.

Renal Impairment

In patients with moderately impaired renal function, dose titration should proceed cautiously (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). In patients with severely impaired renal function (CLcr < 9 mL/min) the use of REMINYL® is not recommended.

Drug-Drug Interactions

Use With Anticholinergics

REMINYL® has the potential to interfere with the activity of anticholinergic medications.

Use With Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect is expected when cholinesterase inhibitors are given concurrently with succinylcholine, other cholinesterase inhibitors, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

A) Effect of Other Drugs on Galantamine

In vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide; CYP2D6 leads to the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged, no single pathway appears predominant.

In vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on day 2 of a 3-day treatment with either cimetidine (800 mg daily) or ranitidine (300 mg daily). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg BID for 4 days, increased the AUC of galantamine by 30%.

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4, at a dose of 500 mg QID for 4 days, affected the AUC of galantamine minimally (10% increase).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, at 20 mg/day for 16 days, increased the oral bioavailability of galantamine by about 40%.

B) Effect of Galantamine on Other Drugs

In vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo

Warfarin: Galantamine at 24 mg/day had no effect on the pharmacokinetics of R- and S-

daily) when they were coadministered. In ... was healthy subject was hospitalized ... degree heart block and bradycardia.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study ... increase in endometrial adenocarcinomas ... 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times ... [AUC] basis) and 30 mg/kg/day (12 times MRHD ... basis or 19 times on an AUC basis). No increase ... the changes was observed in females at ... (equivalent to the MRHD on a mg/m² basis or ... AUC basis) or in males up to the highest ... 30 mg/kg/day (12 times the MRHD on a mg/m² basis).

Galantamine was not carcinogenic in a 6-month ... negativity study in transgenic ... 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (... MRHD on a mg/m² basis and equivalent on an AUC basis). Galantamine produced no evidence of genotoxic potential when evaluated in the in vitro Ames S. typhimurium or E. coli reverse mutation assay, in vitro mouse lymphoma assay, in vivo micronucleus test in mice, or in vitro chromosome aberration assay in Chinese hamster ovary cells. No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis.

There are no adequate and well-controlled studies of REMINYL® in pregnant women. REMINYL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether galantamine is excreted in human breast milk. REMINYL® has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of REMINYL® in children is not recommended.

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience

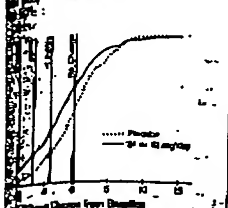
Adverse Events Leading to Discontinuation: In two large scale, placebo-controlled trials of 6 months duration, in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principal reason for discontinuing galantamine. Table 1 shows the most frequent adverse events leading to discontinuation in this study.

Table 1: Most Frequent Adverse Events Leading to Discontinuation in a Placebo-Controlled, Double-Blind Trial With a 4-Week Dose Escalation Schedule

	4-Week Escalation		
Adverse Event	Placebo N=286	16 mg/day N=279	24 mg/day N=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	3%
Dizziness	<1%	2%	<1%
Syncope	0%	0%	1%

Adverse Events ...

...Percentage of Patients Completing ... Treatment with Specified ... in ADAS-cog Scores ... Patients who ... Placebo 30%.



...Change from Baseline

... ADAS-cog	-7	-4	0
...	4.5%	19.4%	60.0%
...	11.9%	32.9%	65.3%

... group was statistically significantly ...

... of CIBIC plus Ratings at Week 13

... patients age, gender, or race did ... of treatment.

... hydrobromide is indicated for ... moderate dementia of the Alzheimer's type.

... hydrobromide is contraindicated ... known hypersensitivity to galantamine ... or to any excipients used in the ...

... inhibitor is likely to exaggerate ... blocking effects of succinylcholine-type ... muscular blocking agents during ...

... action, cholinesterase inhibitors ... effects on the sinoatrial and atrioventricular ... to bradycardia and AV block. ... particularly important to patients ... conduction disorders or to patients ... concomitantly that significantly ... surveillance of marketed ... has shown. However, that ... heart block have been reported ... known underlying cardiac ... Therefore all patients should ... adverse effects on cardiac conduction ...

... bradycardia was reported ... treated patients than in ... led to treatment discontinuation ... of this event was 2-3% for ... compared with <1% for ... of heart block was observed ...

... up to 24 mg/day using ... showed a dose-related increase ... 1.5% (1/286); 4 mg BID ... (18/...), 12 mg BID 2.3% ...

... cholinomimetics may be expected ... secretion due to increased ... should be monitored ... or occult gastrointestinal ... increased risk for developing ... history of ulcer disease or ... anti-inflammatory ... of REMINYL® (galantamine ... increase, relative to ...

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Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4, at a dose of 500 mg QID for 4 days, affected the AUC of galantamine minimally (10% increase).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, at 20 mg/day for 16 days, increased the oral bioavailability of galantamine by about 40%.

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In vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo

Warfarin: Galantamine at 24 mg/day had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time. The protein binding of warfarin was unaffected by galantamine.

daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis) and 30 mg/kg/day (12 times MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the in vitro Ames S. typhimurium or E. coli reverse mutation assay, in vitro mouse lymphoma assay, in vivo micronucleus test in mice, or in vitro chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis.

There are no adequate and well-controlled studies of REMINYL® in pregnant women. REMINYL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether galantamine is excreted in human breast milk. REMINYL® has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of REMINYL® in children is not recommended.

ADVERSE REACTIONS

Pre-Marketing Clinical Trial Experience

Adverse Events Leading to Discontinuation: In two large scale, placebo-controlled trials of 6 months duration, in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects the principle reason for discontinuing galantamine. Table 1 shows the most frequent adverse events leading to discontinuation in this study.

Table 1 Most Frequent Adverse Events Leading to Discontinuation in a Placebo-Controlled, Double-Blind Trial With a 4-Week Dose Escalation Schedule

	4-Week Escalation		
	Placebo	16 mg/day	24 mg/day
Adverse Event	N=286	N=279	N=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	2%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Adverse Events Reported in Controlled Trials: The reported adverse events in REMINYL® (galantamine hydrobromide) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In

Reminyl—Cont.

lirastar may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ.
The majority of these adverse events occurred during the dose-escalation period. In those patients who experienced the most frequent adverse event, nausea, the median duration of the nausea was 5-7 days.
Administration of REMINYL® with food, the use of antiemetic medication, and ensuring adequate fluid intake may reduce the impact of these events.
The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of REMINYL® under conditions of every 4 week dose-escalation for each dose increment of 8 mg/day, are shown in Table 2. These events were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose.

Table 2: The Most Frequent Adverse Events in the Placebo-Controlled Trial With Dose Escalation Every 4 Weeks Occurring in at Least 5% of Patients Receiving REMINYL® and at Least Twice the Rate on Placebo.

	Placebo	REMINYL® 16 mg/day	REMINYL® 24 mg/day
Adverse Event	N=286	N=279	N=273
Nausea	5%	13%	17%
Vomiting	1%	6%	10%
Diarrhea	6%	12%	6%
Anorexia	3%	7%	9%
Weight decrease	1%	5%	5%

Table 3: The most common adverse events (adverse events occurring with an incidence of at least 2% with REMINYL® treatment and in which the incidence was greater than with placebo treatment) are listed in Table 3 for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL®.

Table 3: Adverse Events Reported in at Least 2% of Patients With Alzheimer's Disease Administered REMINYL® and at a Frequency Greater Than With Placebo

Body System Adverse Event	Placebo (N=801)	REMINYL®ª (N=1040)
Body as a whole – general disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & peripheral nervous system disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastrointestinal system disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart rate and rhythm disorders		
Bradycardia	1%	2%
Metabolic and nutritional disorders		
Weight decrease	2%	7%
Psychiatric disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red blood cell disorders		
Anemia	2%	3%
Respiratory system disorders		
Rhinitis	3%	4%
Urinary system disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

ª Adverse events in patients treated with 16 or 24 mg/day of REMINYL® in four placebo-controlled trials are included.

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with REMINYL® treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.
There were no important differences in adverse event rate related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates. No clinically relevant abnormalities in laboratory values were observed.
Other Adverse Events Observed During Clinical Trials
REMINYL® was administered to 3055 patients with Alzheimer's disease. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years.
To establish the rate of adverse events, data from all patients receiving any dose of galantamine in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients; rare adverse events – those occurring in fewer than 1/1000 patients. These adverse events are not necessarily related to REMINYL® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.
Body As a Whole - General Disorders: *Frequent:* chest pain
Cardiovascular System Disorders: *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure
Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia
Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *rare:* esophageal perforation
Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T-wave inversion, ventricular tachycardia
Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased
Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia
Psychiatric Disorders: *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium
Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi
Post-Marketing Experience
Other adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with REMINYL® include:
Body as a Whole – General Disorders: dehydration (including rare, severe cases leading to renal insufficiency and renal failure)
Central & Peripheral Nervous System Disorders: aggression
Gastrointestinal System Disorders: upper and lower GI bleeding
Metabolic & Nutritional Disorders: hypokalemia
These adverse events may or may not be causally related to the drug.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.
As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.
Tertiary anticholinergics such as atropine may be used as an antidote for REMINYL® (galantamine hydrobromide) overdosage. Intravenous atropine sulfate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v. with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether REMINYL® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.
In a postmarketing report, one patient who had been taking 4 mg of galantamine daily for a week inadvertently ingested eight 4 mg tablets (32 mg total) on a single day. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment.

DOSAGE AND ADMINISTRATION

The dosage of REMINYL® (galantamine hydrobromide) shown to be effective in controlled clinical trials [illegible] day given as twice daily dosing. As the dose [illegible] less well tolerated than lower doses and does [illegible] increased effectiveness, the recommended [illegible] 16-24 mg/day given in a BID regimen. The [illegible] day did not provide a statistically significant [illegible] benefit than 16 mg/day. It is possible, however [illegible] dose of 24 mg of REMINYL® might provide [illegible] efit for some patients.
The recommended starting dose of REMINYL® [illegible] twice a day (8 mg/day). The dose should be [illegible] initial maintenance dose of 8 mg twice [illegible] after 4 weeks. If this initial maintenance [illegible] ated, a further increase to 12 mg twice a [illegible] should be attempted only after a minimum [illegible] 8 mg twice a day (16 mg/day). Dose [illegible] based upon assessment of clinical benefit [illegible] the previous dose.
REMINYL® should be administered twice [illegible] with morning and evening meals.
Patients and caregivers should be advised [illegible] quate fluid intake during treatment. If [illegible] terrupted for several days or longer, the [illegible] restarted at the lowest dose and the [illegible] current dose.
Caregivers should be instructed in the [illegible] administering REMINYL® Oral Solution [illegible] should be informed of the existence of [illegible] (included with the product) describing [illegible] be administered. They should be urged [illegible] prior to administering REMINYL® Oral [illegible] ers should direct questions about the [illegible] solution to either their physician or [illegible]
The abrupt withdrawal of REMINYL® [illegible] who had been receiving doses in the [illegible] associated with an increased frequency [illegible] comparison with those continuing to [illegible] of that drug. The beneficial effects of [illegible] however, when the drug is discontinued [illegible]
Doses in Special Populations
Galantamine plasma concentrations [illegible] patients with moderate to severe [illegible] patients with moderately impaired [illegible] Pugh score of 7-9), the dose should [illegible] 16 mg/day. The use of REMINYL® in [illegible] hepatic impairment (Child-Pugh score [illegible] commended.
For patients with moderate renal [illegible] should generally not exceed 16 mg/day [illegible] vere renal impairment (creatinine [illegible] the use of REMINYL® is not recommended [illegible]

HOW SUPPLIED

REMINYL® (galantamine hydrobromide) [illegible] printed "JANSSEN" on one side, [illegible] "4", "8", or "12" on the other.
4 mg off-white tablet: bottles of [illegible]
8 mg pink tablet: bottles of 60 [illegible]
12 mg orange-brown tablet: bottles [illegible]
REMINYL® (galantamine hydrobromide) [illegible] lution (NDC 50458-388-10) is [illegible] plied in 100 mL bottles with a [illegible] milliliters) pipette. The [illegible] 0.5 mL, while the maximum [illegible]
Storage and Handling
REMINYL® tablets should be [illegible] sions permitted to 15-30°C [illegible] Room Temperature].
REMINYL® oral solution should [illegible] excursions permitted to 15-30°C [illegible] trolled Room Temperature]. [illegible] Keep out of reach of children. [illegible]

[illegible] Pat. No. 4,663,318
[illegible] tablets are [illegible] by:
[illegible] Puerto Rico or [illegible] Latina, Italy
[illegible] oral solution [illegible] by:
[illegible] N.V.
[illegible] tablets and oral solution are distributed by: [illegible] Products, L.P. [illegible] 08560

[illegible] REMINYL® [illegible]

[illegible] directions below to use your REMINYL® [illegible] pipette and bottle, unless your doctor gave you [illegible] ctions.
[illegible] Read these instructions before using [illegible] oral solution.
[illegible] bottle and use the pipette (plastic tube) [illegible] with a child-proof cap. Here is how to open [illegible]
[illegible] plastic cap on the bottle down while turning the [illegible] clockwise (to the left) (Figure 1). Remove the [illegible] cap.


FIG. 1

[illegible] out of its case. The pipette is a tube that [illegible] your dose of REMINYL®. Place the [illegible] into the bottle of REMINYL®. (Figures 2a-

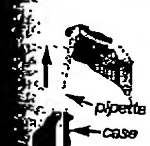


FIG. 2a


FIG. 2b

[illegible] ring of the pipette, pull the pi[illegible] level that equals the dose pre[illegible] Use the markings on the pipette to [illegible] the medicine into the pipette.


FIG. 3b

4. Be careful not to push the plunger in during this step. Hold the bottom ring of the pipette. Remove the entire pipette from the bottle. (Figures 4a-4b)

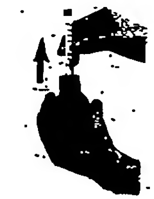


FIG. 4a

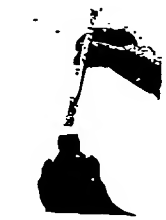


FIG. 4b

5. Empty all the medicine in the pipette into 3–4 ounces (100 mL) of any non alcoholic drink. To do this, push the plunger all the way in. (Figures 5a-5b)


FIG. 5a


FIG. 5b

6. Stir the drink well (Figure 6). Drink all of the mixture right away.
[See figure 6 at top of next column]
7. Replace the plastic cap on the bottle by turning it clockwise (to the right). (Figure 7)
[See figure 7 at top of next column]
8. Rinse the empty pipette by inserting the open end of the [illegible]

The [illegible] that [illegible]
STORAGE [illegible]
25°C (77°F [illegible]
USP Cont[illegible]
NDC 5045[illegible]
REMINYL® [illegible]
(galantamine [illegible]
Oral Solu[illegible]
4 mg/mL
Each 1 mL [illegible]
as equiva[illegible]
1619007
March 200[illegible]
US Patent [illegible]
© Janssen [illegible]
Manufactu[illegible]
Janssen Ph[illegible]
Beerse, Belg[illegible]
Distributed [illegible]
Janssen Pha[illegible]
Titusville, N[illegible]
Shown [illegible]

...t No. 4,663,318
...y 2001
...YL® tablets are
...actured by:
...Gurabo, Puerto Rico or
...Cilag SpA Latina, Italy
...YL® oral solution
...factured by:
...Pharmaceutica N.V.
...Belgium
...YL® tablets and oral solution are distributed by:
...Pharmaceutica Products, L.P.
..., NJ 08560

...YOUR REMINYL®
...DOSE PIPETTE
...UTLY

...e directions below to use your REMINYL® dose pipette and bottle, unless your doctor gave you ...directions.

...NT: Read these instructions before using ...® oral solution.

...the bottle and use the pipette (plastic tube) ...comes with a child-proof cap. Here is how to open ...:

...the plastic cap on the bottle down, while turning the ...counter-clockwise (to the left) (Figure 1). Remove the ...ened cap.

FIG. 1

...pipette out of its case. The pipette is a tube that ...to measure your dose of REMINYL®. Place the ...fully into the bottle of REMINYL®. (Figures 2a-...

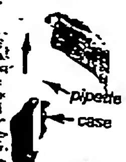


FIG. 2a

FIG. 2b

...bottom ring of the pipette, pull the pi...up to the level that equals the dose pre...Use the markings on the pipette to ...the medicine into the pipette

FIG. 3b

4. Be careful not to push the plunger in during this step. Hold the bottom ring of the pipette. Remove the entire pipette from the bottle. (Figures 4a-4b)

FIG. 4a

FIG. 4b

5. Empty all the medicine in the pipette into 3-4 ounces (100 mL) of any non-alcoholic drink. To do this, push the plunger all the way in. (Figures 5a-5b)

FIG. 5a

FIG. 5b

6. Stir the drink well (Figure 6). Drink all of the solution right away.
(See figure 6 at top of next column)
7. Replace the plastic cap on the bottle by turning it clockwise (to the right). (Figure 7)
(See figure 7 at top of next column)
8. Rinse the empty pipette by inserting it ...

FIG. 6

FIG. 7

pushing the plunger in to remove the water (Figures 8a-8b)

FIG. 8a

FIG. 8b

For more information about REMINYL® see the leaflet that came with the package.

STORAGE: REMINYL® oral solution should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE

NDC 50458-390-10 100 mL

REMINYL®
(galantamine hydrobromide)
Oral Solution
4 mg/mL
Each 1 mL contains 4 mg of galantamine hydrobromide in an aqueous solution.

7619002
March 2003
US Patent No. 4,663,318
© Janssen 2001

Manufactured by:
Janssen Pharmaceutica N.V.
Beerse, Belgium
Distributed by:
Janssen Pharmaceutica Products, L.P.
Titusville, NJ 08560

Monurol—Cont.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term carcinogenicity studies in rodents have not been conducted because MONUROL is intended for single dose treatment in humans. MONUROL was not mutagenic or genotoxic in the in vitro Ames' bacterial reversion test, in cultured human lymphocytes, in Chinese hamster V79 cells, and the in vivo mouse micronucleus assay. MONUROL did not affect fertility or reproductive performance in male and female rats.

Pregnancy: Teratogenic Effects
Pregnancy Category B
When administered intramuscularly as the sodium salt at a dose of 1 gm to pregnant women, fosfomycin crosses the placental barrier. MONUROL crosses the placental barrier of rats; it does not produce teratogenic effects in pregnant rats at dosages as high as 1000 mg/kg/day (approximately 9 and 1.4 times the human dose based on body weight and mg/m[2], respectively). When administered to pregnant female rabbits at dosages as high as 1000 mg/kg/day (approximately 9 and 2.7 times the human dose based on body weight and mg/m[2], respectively), fetotoxicities were observed. However, these toxicities were seen at maternally toxic doses and were considered to be due to the sensitivity of the rabbit to changes in the intestinal microflora resulting from the antibiotic administration. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether fosfomycin tromethamine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MONUROL, a decision should be made whether to discontinue nursing or to not administer the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in children age 12 years and under have not been established in adequate and well-controlled studies.

Geriatric Use: Clinical studies of Monurol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Clinical Trials:
In clinical studies, drug related adverse events which were reported in greater than 1% of the fosfomycin-treated study population are listed below:

Drug-Related Adverse Events (%) in Fosfomycin and Comparator Populations

Adverse Events	Fosfomycin N=1233	Nitrofurantoin N=374	Trimethoprim / sulfamethoxazole N=428	Ciprofloxacin N=445
Diarrhea	9.0	6.6	[illegible]	[illegible]
Vaginitis	5.5	[illegible]	[illegible]	[illegible]
Nausea	[illegible]	[illegible]	[illegible]	[illegible]
Head[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

In clinical trials, the most frequently reported adverse events occurring in >1% of the study population regardless of drug relationship, were:
diarrhea 10.4%, headache 10.3%, vaginitis 7.6%, nausea 5.2%, rhinitis 4.5%, back pain 3.0%, dysmenorrhea 2.6%, pharyngitis 2.5%, dizziness 2.3%, abdominal pain 2.2%, pain 2.2%, dyspepsia 1.8%, asthenia 1.7%, and rash 1.4%.
The following adverse events occurred in clinical trials at a rate of less than 1%, regardless of drug relationship:
abnormal stools, anorexia, constipation, dry mouth, dysuria, ear disorder, fever, flatulence, flu syndrome, hematuria, infection, insomnia, lymphadenopathy, menstrual disorder, migraine, myalgia, nervousness, paresthesia, pruritus, SGPT increased, skin disorder, somnolence, and vomiting. One patient developed unilateral optic neuritis, an event considered possibly related to MONUROL therapy.

Post-marketing Experience:
Serious adverse events from the marketing experience with MONUROL outside of the United States have been rarely reported and include:
angioedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, hepatic necrosis, and toxic megacolon.

Laboratory Changes:
Significant laboratory changes reported in U.S. clinical trials of MONUROL without regard to drug relationship include: increased eosinophil count, increased or decreased WBC count, increased bilirubin, increased SGPT, increased SGOT, increased alkaline phosphatase, decreased hematocrit, decreased hemoglobin, increased and decreased platelet count. The changes were generally transient and were not clinically significant.

OVERDOSAGE

In acute toxicology studies, oral administration of high doses of MONUROL up to 5 gm/kg were well-tolerated in mice and rats, produced transient and minor incidence of watery stool in rabbits, and produced diarrhea with anorexia in dogs occurring in 2–3 days after single dose administration. These doses represent 50–125 times the human therapeutic dose.
There have been no reported cases of overdosage. In the event of overdosage, treatment should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

The recommended dosage for women 18 years of age and older for uncomplicated urinary tract infection (acute cystitis) is one sachet of MONUROL. MONUROL may be taken with or without food.
MONUROL should not be taken in its dry form. Always mix MONUROL with water before ingesting. (See PREPARATION section.)

PREPARATION
MONUROL should be taken orally. Pour the entire contents of a single-dose sachet of MONUROL into 3 to 4 ounces of water (1/2 cup) and stir to dissolve. Do not use hot water. MONUROL should be taken immediately after dissolving in water.

HOW SUPPLIED

MONUROL is available as a single-dose sachet containing the equivalent of 3 grams of fosfomycin.
NDC # 0456-4300-08
Store at controlled room temperature 15° to 30° C (59° to 86°F).
Rx only
Keep this and all drugs out of the reach of children.
Manufactured by:
Zambon S.A.
Division of Zambon Group, SpA
Via Industria
6814 Cadempino, Switzerland
Made in Switzerland
Distributed by:
[illegible]orest Pharmaceuticals, Inc.
[illegible]sidiary of Forest Laboratories, Inc.
[illegible]ouis, MO 63045

[illegible]RENCES

[illegible]onal Committee for Clinical Laboratory Standards, [illegible] for Dilution Antimicrobial Susceptibility Tests for [illegible] that Grow Aerobically — Third Edition; Approved [illegible] NCCLS Document M7-A3, Vol. 13, No. 25 NCCLS, [illegible]a, December, 1993.
2. National Committee for Clinical Laboratory [illegible] Performance Standard for Antimicrobial Disk S[illegible] Tests — Fifth Edition; Approved Standard [illegible] ment M2-A5, Vol. 13, No. 24 NCCLS, Villanova, [illegible] ber, 1993.

CLINICAL STUDIES

In controlled, double-blind studies of acute [illegible] formed in the United States, a single-dose of [illegible] was compared to three other oral antibiotics [illegible] low). The study population consisted of patients [illegible] toms and signs of acute cystitis of less than 4 [illegible] no manifestations of upper tract infection (e.g. [illegible] chills, fever), no history of recurrent urinary tract [illegible] (20% of patients in the clinical studies had a [illegible] acute cystitis within the preceding year), no [illegible] tural abnormalities, and no clinical or laboratory [illegible] of hepatic dysfunction, and no known or suspected [illegible] orders, such as epilepsy, or other factors which [illegible] dispose to seizures. In these studies, the following [illegible] success (resolution of symptoms) and microbiologic [illegible] tion rates were obtained.
[See table at bottom left]

Pathogen	Fosfomycin 3 gm single dose	Ciprofloxacin 250 mg bid × 7d	Trimethoprim/sulfamethoxazole 160 mg/800 mg bid × 10d	[illegible]
E. coli	109/144 (76%)	184/187 (98%)	113/N[illegible] (98%)[illegible]	[illegible]
E. faecalis	10/10 (100%)	0/0	[illegible] (100%)	[illegible]

Clinical [illegible] Rate	Outcome (based on difference in microbiologic eradication rates at 5–11 days post therapy)
[illegible]1 (79%)	
[illegible](96%)	Fosfomycin inferior to ciprofloxacin
[illegible]	Fosfomycin inferior to trimethoprim/sulfamethoxazole
[illegible]	Fosfomycin equivalent to nitrofurantoin

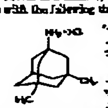
Rev 6/02
Shown in Product Identification Guide[illegible]

NAMENDA™ TABLETS

[nă-mĕn-dă]
(memantine hydrochloride)
Rx Only

DESCRIPTION

NAMENDA™ (memantine hydrochloride) is a[illegible] NMDA receptor antagonist. The chemical [illegible] memantine hydrochloride is 1-amino-3,5-di[illegible] tane hydrochloride with the following struc[illegible]



The molecular formula is $C_{12}H_{21}N \cdot HCl$ and [illegible] weight is 215.76.
Memantine HCl occurs as a fine white p[illegible] and is soluble in water. NAMENDA is ava[illegible] ministration as capsule-shaped, film-coated [illegible] ing 5 mg and 10 mg of memantine hydroch[illegible] lets also contain the following inactive [illegible] microcrystalline cellulose, lactose mono[illegible] silicon dioxide, talc and magnesium ste[illegible] the following inactive ingredients are also [illegible] ponents of the film coat: hypromellose, tri[illegible] dioxide, FD & C yellow #6 and FD & C [illegible] tablets), iron oxide black (10 mg tablets[illegible]

CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacody[illegible]
Persistent activation of central nervous [illegible] D-aspartate (NMDA) receptors by the [illegible] glutamate has been hypothesized to contr[illegible] tomatology of Alzheimer's disease. Mem[illegible] to exert its therapeutic effect through [illegible] moderate affinity uncompetitive (open-[illegible] ceptor antagonist which binds prefer[illegible] receptor-operated cation channels. The[illegible] memantine prevents or slows neurodeg[illegible] with Alzheimer's disease.
Memantine showed low to negligible [illegible] cholinergic, dopamine, adrenergic, [illegible] receptors and for voltage-dependent Ca[illegible] nels. Memantine also showed anta[illegible] 5HT[3] receptor with a potency similar [illegible] receptor and blocked nicotinic acet[illegible] one-sixth to one-tenth the potency[illegible] In vitro studies have shown that [illegible] the reversible inhibition of acetylch[illegible] pezil, galantamine, or tacrine.

Pharmacokinetics
Memantine is well absorbed after [illegible] has linear pharmacokinetics over [illegible] range. It is excreted predominantly [illegible] changed, and has a terminal elim[illegible]

[illegible] Distribution
[illegible] administration, memantine is highly ab[illegible] maximum concentrations reached in about 3–7 hours. [illegible] effect on the absorption of memantine. The [illegible] distribution of memantine is 9–11 L/kg and [illegible] protein binding is low (45%).

[illegible] and Elimination
[illegible] undergoes little metabolism, with the majority [illegible] administered dose excreted unchanged [illegible] remainder is converted primarily to three [illegible]: the N-glucuronide conjugate, 6-hydroxy [illegible] and 1-nitroso-deaminated memantine. These [illegible] minimal NMDA receptor antagonist ac[illegible] microsomal CYP450 enzyme system does [illegible] role in the metabolism of memantine. [illegible] a terminal elimination half-life of about [illegible] renal clearance involves active tubular secre[illegible] by pH dependent tubular reabsorption.

[illegible]: Adequate information on the effect of [illegible] on the pharmacokinetics of memantine is [illegible] As the major route of elimination is renal, [illegible] very likely that subjects with moderate and [illegible] impairment will have significantly higher ex[illegible] normal subjects.
[illegible] pharmacokinetics of NAMENDA in young [illegible] subjects are similar.
[illegible] During multiple dose administration of [illegible] mg b.i.d., females had about 45% higher ex[illegible] males, but there was no difference in exposure [illegible] weight was taken into account.

[illegible] Interactions
[illegible] Microsomal Enzymes: In vitro studies have [illegible] memantine produces minimal inhibition of [illegible] CYP1A2, CYP2A6, CYP2C9, CYP2D6, [illegible] CYP3A4. These data indicate that no phar[illegible] interactions with drugs metabolized by these [illegible] expected.
[illegible] Microsomal Enzymes: Since memantine un[illegible] metabolism, with the majority of the dose [illegible] excreted in urine, an interaction between [illegible] drugs that are inhibitors of CYP450 en[illegible] Coadministration of NAMENDA with the [illegible] donepezil HCl does not affect the pharma[illegible] of either compound.
[illegible] via Renal Mechanisms: Memantine is [illegible] by tubular secretion. In vivo studies have [illegible] single doses of the diuretic hydrochlorothia[illegible] (HCTZ/TA) did not affect the AUC of [illegible] steady state. Memantine did not affect the [illegible] TA, and decreased AUC and C_{max} of HCTZ [illegible].

[illegible] the urine alkaline: The clearance of [illegible] reduced by about 80% under alkaline urine [illegible] 8. Therefore, alterations of urine pH to[illegible] state may lead to an accumulation of the [illegible] increase in adverse effects. Drugs that [illegible] (e.g. carbonic anhydrase inhibitors, so[illegible] would be expected to reduce renal elimi[illegible].

[illegible] to plasma proteins: Because the [illegible] binding of memantine is low (45%), an in[illegible] that are highly bound to plasma pro[illegible] and digoxin, is unlikely.

[illegible]

[illegible] NAMENDA (memantine hydrochloride) [illegible] patients with moderate to severe Alzhei[illegible] demonstrated in 2 randomized, double-[illegible] clinical studies (Studies 1 and 2) [illegible] United States that assessed both cognitive [illegible] daily function. The mean age of patients [illegible] two trials was 76 with a range of [illegible] approximately 66% of patients were female [illegible] were Caucasian.
[illegible] 3), carried out in Latvia, enrolled pa[illegible] dementia, but did not assess cognitive [illegible] endpoint.
[illegible]: In each U.S. study, the effec[illegible] NDA was determined using both an in[illegible] to evaluate overall function through [illegible] assessment, and an instrument that [illegible] Both studies showed that patients on [illegible] significant improvement on both [illegible] placebo.
[illegible] was assessed in both studies using the [illegible] Cooperative Study – Activities [illegible] (ADCS-ADL). The ADCS-ADL [illegible] battery of ADL questions used [illegible] capabilities of patients. Each [illegible] the highest level of independent per[illegible] The investigator performs the in[illegible] caregiver familiar with the be[illegible] of 19 items, including ratings [illegible] eat, dress, bathe, telephone, travel, [illegible] household chores has been vali[illegible] patients with moderate to se[illegible] modified ADCS-ADL, which has a [illegible] with the lower scores indicating [illegible].
[illegible] to improve cognitive performance [illegible] with the Severe Impairment [illegible] instrument that has been vali[illegible] with moderate to severe dementia. The SIB examines selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

Study 1 (Twenty-Eight-Week Study)
In a study of 28 weeks duration, 252 patients with moderate to severe probable Alzheimer's disease (diagnosed by DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥3 and ≤14 and Global Deterioration Scale Stages 5-6) were randomized to NAMENDA or placebo. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Effects on the ADCS-ADL:
Figure 1 shows the time course for the change from baseline in the ADCS-ADL score for patients in the two treatment groups completing the 28 weeks of the study. At 28 weeks of treatment, the mean difference in the ADCS-ADL change scores for the NAMENDA-treated patients compared to the patients on placebo was 3.4 units. Using an analysis based on all patients and carrying their last study observation forward (LOCF analysis), NAMENDA treatment was statistically significantly superior to placebo.

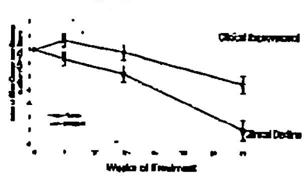


Figure 1. Time course of the change from baseline in ADCS-ADL score for patients completing 28 weeks of treatment.

Figure 2 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the change in the ADCS-ADL shown on the X axis. The curves show that both patients assigned to NAMENDA and placebo have a wide range of responses and generally show deterioration (a negative change in ADCS-ADL compared to baseline), but that the NAMENDA group is more likely to show a smaller decline or an improvement. (In a cumulative distribution display, a curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo.)

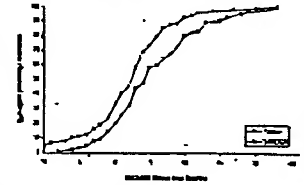


Figure 2. Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB:
Figure 3 shows the time course for the change from baseline in SIB score for the two treatment groups over the 28 weeks of the study. At 28 weeks of treatment, the mean difference in the SIB change scores for the NAMENDA-treated patients compared to the patients on placebo was 5.7 units. Using an LOCF analysis, NAMENDA treatment was statistically significantly superior to placebo.

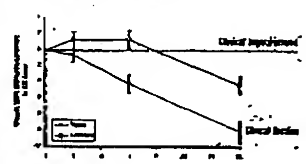


Figure 3. Time course of the change from baseline in SIB score for patients completing 28 weeks of treatment.

Figure 4 shows the cumulative percentages of patients from each treatment group who had attained at least the mea[illegible]

The curves show that both patients assigned to NAMENDA and placebo have a wide range of responses and generally show deterioration, but that the NAMENDA group is more likely to show a smaller decline or an improvement.

Figure 4: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 2 (Twenty-Four-Week Study)
In a study of 24 weeks duration, 404 patients with moderate to severe probable Alzheimer's disease (diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥5 and ≤14) who had been treated with donepezil for at least 6 months and who had been on a stable dose of donepezil for the last 3 months were randomized to NAMENDA or placebo while still receiving donepezil. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Effects on the ADCS-ADL:
Figure 5 shows the time course for the change from baseline in the ADCS-ADL score for the two treatment groups over the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the ADCS-ADL change scores for the NAMENDA/donepezil treated patients (combination therapy) compared to the patients on placebo/donepezil (monotherapy) was 1.6 units. Using an LOCF analysis, NAMENDA/donepezil treatment was statistically significantly superior to placebo/donepezil.

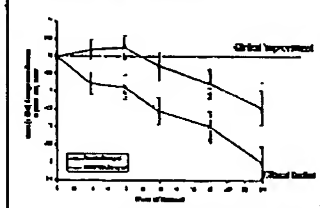


Figure 5: Time course of the change from baseline in ADCS-ADL score for patients completing 24 weeks of treatment.

Figure 6 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the measure of improvement in the ADCS-ADL shown on the X axis.
The curves show that both patients assigned to NAMENDA/donepezil and placebo/donepezil have a wide range of responses and generally show deterioration, but that the NAMENDA/donepezil group is more likely to show a smaller decline or an improvement.

Figure 6: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB:
Figure 7 shows the time course for the change from baseline in SIB score for the two treatment groups over the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the SIB change scores for the NAMENDA/donepezil-treated patients compared to the patients on placebo/donepezil was 3.3 units. Using an LOCF analysis, NAMENDA/[illegible]

Absorption and Distribution

Following oral administration memantine is highly absorbed. Peak concentrations are reached in about 3-7 hours. Food has no effect on the absorption of memantine. The mean volume of distribution of memantine is 9-11 L/kg and plasma protein binding is low (45%).

Metabolism and Elimination

Memantine undergoes little metabolism, with the majority (57-82%) of an administered dose excreted unchanged in urine; the remainder is converted primarily to three polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsomal CYP450 enzyme system does not play a significant role in the metabolism of memantine. Memantine has a terminal elimination half-life of about 60-80 hours. Renal clearance involves active tubular secretion moderated by pH dependent tubular reabsorption.

Special Populations

Renal Impairment: Adequate information on the effect of renal impairment on the pharmacokinetics of memantine is not available. As the major route of elimination is renal, it is very likely that subjects with moderate and severe renal impairment will have significantly higher exposure and increased effects.

Gender: The pharmacokinetics of NAMENDA in young and elderly subjects are similar.

Gender: Following multiple dose administration of memantine 20 mg b.i.d., females had about 45% higher exposure than males, but there was no difference in exposure when body weight was taken into account.

Drug-Drug Interactions

Effect of Microsomal Enzymes: In vitro studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4. These data indicate that no pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effect of Microsomal Enzymes: Since memantine undergoes minimal metabolism, with the majority of the dose excreted unchanged in urine, an interaction between memantine and drugs that are inhibitors of CYP450 enzymes is unlikely. Coadministration of NAMENDA with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound.

Drugs Eliminated via Renal Mechanisms: Memantine is eliminated in part by tubular secretion. In vivo studies have shown that multiple doses of the diuretic hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the AUC of memantine at steady state. Memantine did not affect the bioavailability of TA, and decreased AUC and C_{max} of HCTZ by about 20%.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Drugs that alkalinize the urine (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) would be expected to reduce renal elimination of memantine.

Drugs highly bound to plasma proteins: Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely.

CLINICAL TRIALS

The effectiveness of NAMENDA (memantine hydrochloride) as a treatment for patients with moderate to severe Alzheimer's disease was demonstrated in 2 randomized, double-blind, placebo-controlled clinical studies (Studies 1 and 2) conducted in the United States that assessed both cognitive function and day to day function. The mean age of patients participating in these two trials was 76 with a range of 50-93 years. Approximately 66% of patients were female and 91% of patients were Caucasian.

A third study (Study 3), carried out in Latvia, enrolled patients with severe dementia, but did not assess cognitive function as a planned endpoint.

Study Outcome Measures: In each U.S. study, the effectiveness of NAMENDA was determined using both an instrument designed to evaluate overall function through caregiver-related assessment, and an instrument that measures cognition. Both studies showed that patients on NAMENDA experienced significant improvement on both measures compared to placebo.

Day-to-day function was assessed in both studies using the modified Alzheimer's disease Cooperative Study - Activities of Daily Living inventory (ADCS-ADL). The ADCS-ADL consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The investigator performs the inventory by interviewing a caregiver familiar with the behavior of the patient. A subset of 19 items, including ratings of the patient's ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores has been validated for the assessment of patients with moderate to severe dementia. This is the modified ADCS-ADL, which has a scoring range of 0 to 54, with the lower scores indicating greater functional impairment.

The ability of NAMENDA to improve cognitive performance was assessed in both studies with the Severe Impairment Battery (SIB), a multi-item instrument that has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. The SIB examines selected aspects of cognitive performance, including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment.

Study 1 (Twenty-Eight-Week Study)

In a study of 28 weeks duration, 252 patients with moderate to severe probable Alzheimer's disease (diagnosed by DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥3 and ≤14 and Global Deterioration Scale Stages 5-6) were randomized to NAMENDA or placebo. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

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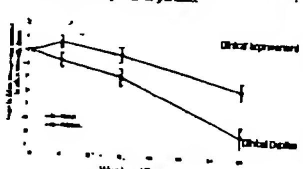


Figure 1: Time course of the change from baseline in ADCS-ADL score for patients completing 28 weeks of treatment.

Figure 2 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the change in the ADCS-ADL shown on the X axis. The curves show that both patients assigned to NAMENDA and placebo have a wide range of responses and generally show deterioration (a negative change in ADCS-ADL compared to baseline), but that the NAMENDA group is more likely to show a smaller decline or an improvement. (In a cumulative distribution display, a curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo.)

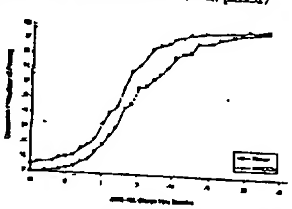


Figure 2: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB:

Figure 3 shows the time course for the change from baseline in SIB score for the two treatment groups over the 28 weeks of the study. At 28 weeks of treatment, the mean difference in the SIB change scores for the NAMENDA-treated patients compared to the patients on placebo was 5.7 units. Using an LOCF analysis, NAMENDA treatment was statistically significantly superior to placebo.

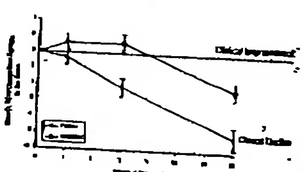


Figure 3. Time course of the change from baseline in SIB score for patients completing 28 weeks of treatment.

Figure 4 shows the cumulative percentages of patients from each treatment group who had attained at least the measure of improvement in the SIB score shown on the X axis.

The curves show that both patients assigned to NAMENDA and placebo have a wide range of responses and generally show deterioration, but that the NAMENDA group is more likely to show a smaller decline or an improvement.

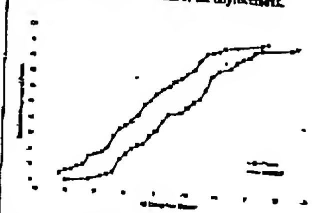


Figure 4: Cumulative percentage of patients completing 28 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 2 (Twenty-Four-Week Study)

In a study of 24 weeks duration, 404 patients with moderate to severe probable Alzheimer's disease (diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥5 and ≤14) who had been treated with donepezil for at least 6 months and who had been on a stable dose of donepezil for the last 3 months were randomized to NAMENDA or placebo while still receiving donepezil. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Effects on the ADCS-ADL:

Figure 5 shows the time course for the change from baseline in the ADCS-ADL score for the two treatment groups over the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the ADCS-ADL change scores for the NAMENDA/donepezil treated patients (combination therapy) compared to the patients on placebo/donepezil (monotherapy) was 1.6 units. Using an LOCF analysis, NAMENDA/donepezil treatment was statistically significantly superior to placebo/donepezil.

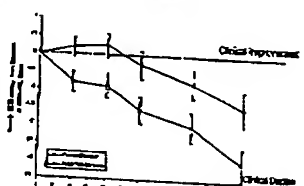


Figure 5: Time course of the change from baseline in ADCS-ADL score for patients completing 24 weeks of treatment.

Figure 6 shows the cumulative percentages of patients from each of the treatment groups who had attained at least the measure of improvement in the ADCS-ADL shown on the X axis.

The curves show that both patients assigned to NAMENDA/donepezil and placebo/donepezil have a wide range of responses and generally show deterioration, but that the NAMENDA/donepezil group is more likely to show a smaller decline or an improvement.

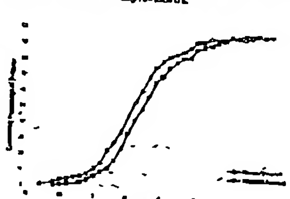


Figure 6: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in ADCS-ADL scores.

Effects on the SIB:

Figure 7 shows the time course for the change from baseline in SIB score for the two treatment groups over the 24 weeks of the study. At 24 weeks of treatment, the mean difference in the SIB change scores for the NAMENDA/donepezil-treated patients compared to the patients on placebo/donepezil was 3.3 units. Using [illegible]

donepezil treatment was statistically significantly superior to placebo/donepezil.

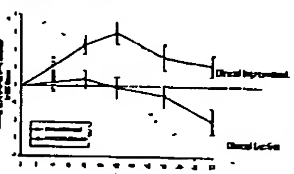


Figure 7: Time course of the change from baseline in SIB score for patients completing 24 weeks of treatment.

Figure 8 shows the cumulative percentages of patients from each treatment group who had attained at least the measure of improvement in SIB score shown on the X axis.

The curves show that both patients assigned to NAMENDA/donepezil and placebo/donepezil have a wide range of responses, but that the NAMENDA/donepezil group is more likely to show an improvement or a smaller decline.

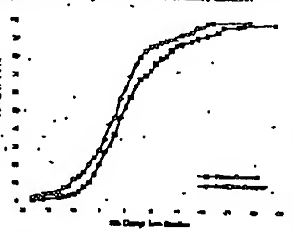


Figure 8: Cumulative percentage of patients completing 24 weeks of double-blind treatment with specified changes from baseline in SIB scores.

Study 3 (Twelve-Week Study)

In a double-blind study of 12 weeks duration, conducted in nursing homes in Latvia, 166 patients with dementia according to DSM-III-R, a Mini-Mental State Examination score of <10, and Global Deterioration Scale staging of 5 to 7 were randomized to either NAMENDA or placebo. For patients randomized to NAMENDA, treatment was initiated at 5 mg once daily and increased to 10 mg once daily after 1 week. The primary efficacy measures were the care dependency subscale of the Behavioral Rating Scale for Geriatric Patients (BGP), a measure of day-to-day function, and a Clinical Global Impression of Change (CGI-C), a measure of overall clinical effect. No valid measure of cognitive function was used in this study. A statistically significant treatment difference at 12 weeks that favored NAMENDA over placebo was seen on both primary efficacy measures. Because the patients entered were a mixture of Alzheimer's disease and vascular dementia, an attempt was made to distinguish the two groups and all patients were later designated as having either vascular dementia or Alzheimer's disease, based on their scores on the Hachinski Ischemic Scale at study entry. Only about 50% of the patients had computerized tomography of the brain. For the subset designated as having Alzheimer's disease, a statistically significant treatment effect favoring NAMENDA over placebo at 12 weeks was seen on both the BGP and CGI-C.

INDICATIONS AND USAGE

NAMENDA (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS

NAMENDA (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS

Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions

Seizures: NAMENDA has not been systematically evaluated in patients with a seizure disorder. In clinical trials of NAMENDA, seizures occurred in 0.2% of patients treated with NAMENDA and 0.5% of patients treated with placebo.

Genitourinary Conditions

Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations

Hepatic Impairment

NAMENDA undergoes partial hepatic metabolism, but the major fraction of a dose (57-82%) is excreted unchanged in urine. The pharmacokinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.

Renal Impairment

There are inadequate data available in patients with mild, moderate, and severe renal impairment but it is likely that patients with moderate renal impairment will have higher exposure than normal subjects. Dose reduction in these patients should be considered. The use of NAMENDA in patients with severe renal impairment is not recommended.

Drug-Drug Interactions

N-methyl-D-aspartate (NMDA) antagonists: The combined use of NAMENDA with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of NAMENDA on substrates of microsomal enzymes: In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on NAMENDA: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Coadministration of NAMENDA with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of NAMENDA and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Carcinogenesis, Mutagenesis and Impairment of Fertility

There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the in vitro *S. typhimurium* or *E. coli* reverse mutation assay, an in vitro chromosomal aberration test in human lymphocytes, an in vivo cytogenetics assay for chromosome damage in rats, and the in vivo mouse micronucleus assay. The results were equivocal in an in vitro gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy

Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the postpartum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

ADVERSE REACTIONS

The experience described in this section derives [illegible] ies in patients with Alzheimer's disease and [illegible] mentia.

Adverse Events Leading to Discontinuation: In [illegible] controlled trials in which dementia patients [illegible] of NAMENDA up to 20 mg/day, the likelihood of [illegible] ation because of an adverse event was the [illegible] NAMENDA group as in the placebo group. No [illegible] adverse event was associated with the discontinuation of treatment in 1% or more of NAMENDA-treated [illegible] and at a rate greater than placebo.

Adverse Events Reported in Controlled Trials: [illegible] ported adverse events in NAMENDA (memantine hydro-chloride) trials reflect experience gained under [illegible] itored conditions in a highly selected patient [illegible] actual practice or in other clinical trials, these [illegible] timates may not apply, as the conditions of [illegible] behavior and the types of patients treated may [illegible] 1 lists treatment-emergent signs and symptoms [illegible] reported in at least 2% of patients in placebo-[illegible] mentia trials and for which the rate of occurrence was greater for patients treated with NAMENDA than [illegible] treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo [illegible]

Table 1: Adverse Events Reported in Controlled Trials in at Least 2% of Patients Receiving NAMENDA and at a Higher Frequency than Placebo-treated [illegible]

Body System / Adverse Event	Placebo (N = 922) %	[illegible]
Body as a Whole		
Fatigue	1	[illegible]
Pain	1	[illegible]
Cardiovascular System		
Hypertension	2	[illegible]
Central and Peripheral Nervous System		
Dizziness	5	[illegible]
Headache	3	[illegible]
Gastrointestinal System		
Constipation	3	[illegible]
Vomiting	2	[illegible]
Musculoskeletal System		
Back pain	2	[illegible]
Psychiatric Disorders		
Confusion	5	[illegible]
Somnolence	2	[illegible]
Hallucination	2	[illegible]
Respiratory System		
Coughing	3	[illegible]
Dyspnea	1	[illegible]

Other adverse events occurring with [illegible] least 2% in NAMENDA-treated patients [illegible] or equal rate on placebo were agitation, [illegible] jury, urinary incontinence, diarrhea, [illegible] nia, urinary tract infection, fall occurred [illegible] abnormal, depression, upper respiratory [illegible] anxiety, peripheral edema, nausea, [illegible] gia.

The overall profile of adverse events and [illegible] for individual adverse events in the [illegible] tients with moderate to severe Alzheimer's [illegible] different from the profile and incidence [illegible] above for the overall dementia population.

Vital Sign Changes: NAMENDA and [illegible] compared with respect to (1) mean change [illegible] vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with NAMENDA. A comparison of supine and standing vital sign measures for NAMENDA and placebo in [illegible] subjects indicated that NAMENDA [illegible] ated with orthostatic changes.

Laboratory Changes: NAMENDA [illegible] were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses [illegible] in laboratory test parameters associated with NAMENDA treatment.

ECG Changes: NAMENDA and placebo groups were compared with respect to (1) mean change from baseline in variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no important changes in ECG parameters associated with NAMENDA treatment.

Other Adverse Events Observed During Clinical Trials

NAMENDA has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received NAMENDA treatment for periods of up to 884 days, with [illegible] receiving at least 24 weeks of treatment and [illegible] receiving 48 weeks or more of treatment.

Treatment-emergent signs and symptoms that occurred during [illegible] controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to NAMENDA treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: *Frequent:* syncope. *Infrequent:* hypothermia, allergic reaction.

Cardiovascular System: *Frequent:* cardiac failure. *Infrequent:* angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent:* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

Gastrointestinal System: *Infrequent:* gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: *Frequent:* anemia. *Infrequent:* leukopenia.

Metabolic and Nutritional Disorders: *Frequent:* increased alkaline phosphatase, decreased weight. *Infrequent:* dehydration, hyponatremia, aggravated diabetes mellitus.

Psychiatric Disorders: *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoid reaction, thinking abnormal, crying abnormal, appetite increased, paroniria, delirium, depersonalization, neurosis, suicide attempt.

Respiratory System: *Frequent:* pneumonia. *Infrequent:* apnea, asthma, hemoptysis.

Skin and Appendages: *Frequent:* rash. *Infrequent:* skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

Special Senses: *Frequent:* cataract, conjunctivitis. *Infrequent:* macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retinal detachment.

Urinary System: *Frequent:* frequent micturition. *Infrequent:* dysuria, hematuria, urinary retention.

Events Reported Subsequent to the Marketing of NAMENDA, Both US and Ex-US: [illegible]

EVENTS FROM OTHER SOURCES

Memantine has been commercially available outside the U.S. since 1982, and has been evaluated in clinical trials in patients with neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity. [illegible] events of possible importance for [illegible] adequate data to determine the causal relationship [illegible] reported to be temporally associated with treatment in more than one patient and [illegible] elsewhere in labeling: acne, bone fracture, [illegible], claudication, hyperlipidemia, [illegible], thrombocytopenia.

ANIMAL TOXICOLOGY

[illegible] increased lesions (vacuolation and necrosis) in multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices, similar to those which are known to occur in rodents administered other NMDA receptor antagonists, were seen after a single dose of memantine. [illegible] rats were given daily oral doses of [illegible] the no-effect dose for neuronal necrosis was [illegible] times the maximum recommended human dose [illegible] potential for induction of central neuronal necrosis by NMDA receptor antagonists in humans is unknown.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an overdose with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

DOSAGE AND ADMINISTRATION

The dosage of NAMENDA (memantine hydrochloride) shown to be effective in controlled clinical trials is 20 mg/day.

The recommended starting dose of NAMENDA is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week.

NAMENDA can be taken with or without food.

Doses in Special Populations

Dose reduction in patients with moderate renal impairment should be considered. In patients with severe renal impairment the use of NAMENDA has not been systematically evaluated and is not recommended. (See Clinical Pharmacology-Pharmacokinetics)

HOW SUPPLIED

5 mg Tablet:
Bottle of 60 NDC #0456-3205-60
10 × 10 Unit Dose NDC #0456-3205-63

The capsule-shaped, film-coated tablets are tan, with the strength (5) debossed on one side and FL on the other.

10 mg Tablet:
Bottle of 60 NDC #0456-3210-60
10 × 10 Unit Dose NDC #0456-3210-63

The capsule-shaped, film coated tablets are gray, with the strength (10) debossed on one side and FL on the other.

Titration Pak:
PVC/Aluminum Blister package containing 49 tablets, 28 × 5 mg and 21 × 10 mg tablets, NDC #0456-3200-14

The 5 mg capsule-shaped, film-coated tablets are tan, with the strength (5) debossed on one side and FL on the other. The 10 mg capsule-shaped, film-coated tablets are gray, with the strength (10) debossed on one side and FL on the other.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045
Licensed from Merz Pharmaceuticals GmbH
10/03

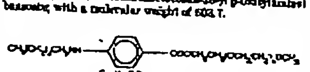
TESSALON®

(benzonatate, USP)
100 mg Perles/
200 mg Capsules
℞ only

℞

DESCRIPTION

TESSALON, a non-narcotic oral antitussive agent, is 2, 5, 8, 11, 14, 17, 20, 23, 26-nonaoxaoctacosan-28-yl p-(butylamino) benzoate; with a molecular weight of 603.7.



Each TESSALON Perle contains:
Benzonatate, USP 100 mg

Each TESSALON Capsule contains:
Benzonatate, USP 200 mg

TESSALON Capsules also contain: D&C Yellow 10, gelatin, glycerin, methylparaben and propylparaben.

CLINICAL PHARMACOLOGY

TESSALON acts peripherally by anesthetizing the stretch receptors located in the respiratory passages, lungs, and pleura by dampening their activity and thereby reducing the cough reflex at its source. It begins to act within 15 to 20 minutes and its effect lasts for 3 to 8 hours. TESSALON has no inhibitory effect on the respiratory center in recommended dosage.

INDICATIONS AND USAGE

TESSALON is indicated for the symptomatic relief of cough.

CONTRAINDICATIONS

[illegible]

WARNINGS

Severe hypersensitivity reactions (including bronchospasm, laryngospasm and cardiovascular collapse) have been reported which are possibly related to local anesthesia from sucking or chewing the perle instead of swallowing it. Severe reactions have required intervention with vasopressor agents and supportive measures.

Isolated instances of bizarre behavior, including mental confusion and visual hallucinations, have also been reported in patients taking TESSALON in combination with other prescribed drugs.

PRECAUTIONS

Benzonatate is chemically related to anesthetic agents of the para-amino-benzoic acid class (e.g., procaine; tetracaine) and has been associated with adverse CNS effects possibly related to a prior sensitivity to related agents or interaction with concomitant medication.

Information for Patients: Release of TESSALON from the capsule in the mouth can produce a temporary local anesthesia of the oral mucosa and choking could occur. Therefore, the capsules should be swallowed without chewing.

Usage in Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with TESSALON. It is also not known whether TESSALON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TESSALON should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when TESSALON is administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity, and reproduction studies have not been conducted with TESSALON.

Pediatric Use: Safety and effectiveness in children below the age of 10 has not been established.

ADVERSE REACTIONS

Potential Adverse Reactions to TESSALON may include:
Hypersensitivity reactions including bronchospasm, laryngospasm, cardiovascular collapse possibly related to local anesthesia from chewing or sucking the capsule.
CNS: sedation; headache; dizziness; mental confusion; visual hallucinations.
GI: constipation, nausea, GI upset.
Dermatologic: pruritus; skin eruptions.
Other: nasal congestion; sensation of burning in the eyes; vague "chilly" sensation; numbness of the chest; hypersensitivity.

Rare instances of deliberate or accidental overdose have resulted in death.

OVERDOSAGE

Overdose may result in death.

The drug is chemically related to tetracaine and other topical anesthetics and shares various aspects of their pharmacology and toxicology. Drugs of this type are generally well absorbed after ingestion.

Signs and Symptoms:

If capsules are chewed or dissolved in the mouth, oropharyngeal anesthesia will develop rapidly. CNS stimulation may cause restlessness and tremors which may proceed to clonic convulsions followed by profound CNS depression.

Treatment:

Evacuate gastric contents and administer copious amounts of activated charcoal slurry. Even in the conscious patient, cough and gag reflexes may be so depressed as to necessitate special attention to protection against aspiration of gastric contents and orally administered materials. Convulsions should be treated with a short-acting barbiturate given intravenously and carefully titrated for the smallest effective dosage. Intensive support of respiration and cardiovascular-renal function is an essential feature of the treatment of severe intoxication from overdosage.

Do not use CNS stimulants.

DOSAGE AND ADMINISTRATION

Adults and Children over 10: Usual dose is one 100 mg or 200 mg capsule t.i.d. as required. If necessary, up to 600 mg daily may be given.

HOW SUPPLIED

Perles, 100 mg (yellow); bottles of 100
NDC 0456-0688-01 Imprint: T.
Perles, 100 mg (yellow); bottles of 500
NDC 0456-0688-02 Imprint: T.
Capsules, 200 mg (yellow); bottles of 100
NDC 0456-0698-01 Imprint: 0698
Capsules, 200 mg (yellow); bottles of 500
NDC 0456-0698-02 Imprint: 0698

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Rev. 3/03 (04)

Mfd by
Cardinal Health
St. Petersburg, Florida 33716
for
FOREST PHARMACEUTICALS, INC.
SUBSIDIARY OF FOREST LABORATORIES, INC.
ST. LOUIS, MISSOURI 63045

Shown in Product Identification Guide, page 312

...in laboratory test parameters associated with ...DA treatment.
... NAMENDA and placebo groups were compared ... mean change from baseline in vital ... and ... the incidence of patients meeting ... potentially clinically significant changes ... these variables. These analyses revealed no ... changes in ECG parameters associated with ... treatment.

...Events Observed During Clinical Trials

...has been administered to approximately 1350 ... dementia, of whom more than 1200 received ... recommended dose of 20 mg/day. Patients received ...NDA treatment for periods of up to 884 days, ... received at least 24 weeks of treatment ... received 48 weeks or more of treatment. ...emergent signs and symptoms that occurred ...controlled clinical trials and 4 open label trials ... as adverse events by the clinical investigators ... of their own choosing. To provide an ... of the proportion of individuals having similar ... the events were grouped into a smaller ... standardized categories using WHO terminology ... were calculated across all studies.

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...: *Frequent:* syncope. *Infrequent:* hypothermia...

...System: *Frequent:* cardiac failure. *Infrequent:* ... bradycardia, myocardial infarction, ... atrial fibrillation, hypotension, cardiac ... hypotension, pulmonary embolism, pulmonary ...

...Peripheral Nervous System: *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ... *Infrequent:* paresthesia, convulsions, ... disorder, hypertonia, tremor, aphasia, hypo... coordination, hemiplegia, hyperkinesia, ... contractions, stupor, cerebral hemorrhage, ... neuropathy.

...System: *Infrequent:* gastroenteritis, diverticulitis, ... intestinal hemorrhage, melena, esophageal ...

...Disorders: *Frequent:* anemia. *Infrequent:* ...

...Nutritional Disorders: *Frequent:* increased ... increased weight. *Infrequent:* dehydration, aggravated diabetes mellitus.

...Disorders: *Frequent:* aggressive reaction. *Infrequent:* ... personality disorder, emotional lability, ... disorder, libido increased, psychosis, ... paranoid reaction, thinking abnormal, crying ... increased, paroniria, delirium, depersonalization, ... attempt.

...System: *Frequent:* pneumonia. *Infrequent:* ...

...: *Frequent:* rash. *Infrequent:* skin ulceration, ... pruritus, eczema, dermatitis, erythematous ...

...: *Frequent:* cataract, conjunctivitis. *Infrequent:* ... degeneration, decreased visual acuity, ... blepharitis, blurred vision, corneal ..., conjunctival hemorrhage, eye pain, ... diplopia, abnormal ... retinal detachment.

...: *Frequent:* frequent micturition. *Infrequent:* ... urinary retention.

...FROM OTHER SOURCES

...has been commercially available outside the U.S. ... and has been evaluated in clinical trials in patients with neuropathic pain ... organic brain syndrome, and spasticity ... events of possible importance for ... data to determine the causal relationship ... reported to be temporally associated with ... treatment in more than one patient and ... elsewhere in labeling: acute bone fracture, ... classification, hyperlipidemia, ... thrombocytopenia.

...OLOGY

...animal lesions (vacuolation and necrosis) ... and pyramidal cells in cortical layers ... the posterior cingulate and retrosplenial ... similar to those which are known to occur ... other NMDA receptor antagonists ... after a single dose of memantine ... was given daily and doses of ... the no-effect dose for neuronal ... recommended human dose ... potential for induction of central neuro... by NMDA receptor antagonists.

...AND DEPENDENCE

...: Memantine HCl is not a con...

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug.

As in any case of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine. In a documented case of an overdosage with up to 400 mg of memantine, the patient experienced restlessness, psychosis, visual hallucinations, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae.

DOSAGE AND ADMINISTRATION

The dosage of NAMENDA (memantine hydrochloride) shown to be effective in controlled clinical trials is 20 mg/day.

The recommended starting dose of NAMENDA is 5 mg once daily. The recommended target dose is 20 mg/day. The dose should be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (5 mg and 10 mg as separate doses), and 20 mg/day (10 mg twice a day). The minimum recommended interval between dose increases is one week. NAMENDA can be taken with or without food.

Doses in Special Populations

Dose reduction in patients with moderate renal impairment should be considered. In patients with severe renal impairment the use of NAMENDA has not been systematically evaluated and is not recommended. (See Clinical Pharmacology-Pharmacokinetics)

HOW SUPPLIED

5 mg Tablet:

Bottle of 60	NDC #0456-3205-60
10 × 10 Unit Dose	NDC #0456-3205-63

The capsule-shaped, film-coated tablets are tan, with the strength (5) debossed on one side and FL on the other.

10 mg Tablet:

Bottle of 60	NDC #0456-3210-60
10 × 10 Unit Dose	NDC #0456-3210-63

The capsule-shaped, film-coated tablets are gray, with the strength (10) debossed on one side and FL on the other

Titration Pak:

PVC/Aluminum Blister package containing 49 tablets, 28 × 5 mg and 21 × 10 mg tablets. NDC #0456-3200-14

The 5 mg capsule-shaped, film coated tablets are tan, with the strength (5) debossed on one side and FL on the other. The 10 mg capsule-shaped, film-coated tablets are gray with the strength (10) debossed on one side and FL on the other.

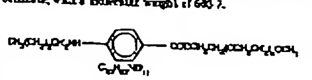
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045
Licensed from Merz Pharmaceuticals GmbH
10/03

TESSALON®
(Benzonatate, USP)
100 mg Perles/
200 mg Capsules
℞ only ℞

DESCRIPTION

TESSALON, a non-narcotic oral antitussive agent, is 2, 5, 8, 11, 14, 17, 20, 23, 26-nonaoxaoctacosan-28-yl p-(butylamino) benzoate; with a molecular weight of 603.7.



Each TESSALON Perle contains:
Benzonatate, USP ... 100 mg
Each TESSALON Capsule contains:
Benzonatate, USP ... 200 mg

TESSALON Capsules also contain: D&C Yellow 10, gelatin, glycerin, methylparaben and propylparaben.

CLINICAL PHARMACOLOGY

TESSALON acts peripherally by anesthetizing the stretch receptors located in the respiratory passages, lungs, and pleura by dampening their activity and thereby reducing the cough reflex at its source. It begins to act within 15 to 20 minutes and its effect lasts for 3 to 8 hours. TESSALON has no inhibitory effect on the respiratory center in recommended dosage.

INDICATIONS AND USAGE

TESSALON is indicated for the symptomatic relief of cough.

CONTRAINDICATIONS

Hypersensitivity to benzonatate or related ...

WARNINGS

Severe hypersensitivity reactions (including bronchospasm, laryngospasm and cardiovascular collapse) have been reported which are possibly related to local anesthesia from sucking or chewing the perle instead of swallowing it. Severe reactions have required intervention with vasopressor agents and supportive measures.

Isolated instances of bizarre behavior, including mental confusion and visual hallucinations, have also been reported in patients taking TESSALON in combination with other prescribed drugs.

PRECAUTIONS

Benzonatate is chemically related to anesthetic agents of the para-amino-benzoic acid class (e.g., procaine; tetracaine) and has been associated with adverse CNS effects possibly related to a prior sensitivity to related agents or interaction with concomitant medication.

Information for Patients: Release of TESSALON from the capsule in the mouth can produce a temporary local anesthesia of the oral mucosa and choking could occur. Therefore, the capsules should be swallowed without chewing.

Usage in Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with TESSALON. It is also not known whether TESSALON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TESSALON should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when TESSALON is administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity, and reproduction studies have not been conducted with TESSALON.

Pediatric Use: Safety and effectiveness in children below the age of 10 has not been established.

ADVERSE REACTIONS

Potential Adverse Reactions to TESSALON may include:
Hypersensitivity reactions including bronchospasm, laryngospasm, cardiovascular collapse possibly related to local anesthesia from chewing or sucking the capsule.
CNS: sedation; headache; dizziness; mental confusion; visual hallucinations.
GI: constipation, nausea, GI upset.
Dermatologic: pruritus; skin eruptions.
Other: nasal congestion; sensation of burning in the eyes; vague "chilly" sensation; numbness of the chest; hypersensitivity.

Rare instances of deliberate or accidental overdose have resulted in death.

OVERDOSAGE

Overdose may result in death.

The drug is chemically related to tetracaine and other topical anesthetics and shares various aspects of their pharmacology and toxicology. Drugs of this type are generally well absorbed after ingestion.

Signs and Symptoms:
If capsules are chewed or dissolved in the mouth, oropharyngeal anesthesia will develop rapidly. CNS stimulation may cause restlessness and tremors which may proceed to clonic convulsions followed by profound CNS depression.

Treatment:
Evacuate gastric contents and administer copious amounts of activated charcoal slurry. Even in the conscious patient, cough and gag reflexes may be so depressed as to necessitate special attention to protection against aspiration of gastric contents and orally administered materials. Convulsions should be treated with a short-acting barbiturate given intravenously and carefully titrated for the smallest effective dosage. Intensive support of respiration and cardiovascular-renal function is an essential feature of the treatment of severe intoxication from overdosage.
Do not use CNS stimulants.

DOSAGE AND ADMINISTRATION

Adults and Children over 10: Usual dose is one 100 mg or 200 mg capsule t.i.d. as required. If necessary, up to 600 mg daily may be given.

HOW SUPPLIED

Perles, 100 mg (yellow); bottles of 100
NDC 0456-0688-01 Imprint: T
Perles, 100 mg (yellow); bottles of 500
NDC 0456-0688-02 Imprint: T
Capsules, 200 mg (yellow); bottles of 100
NDC 0456-0698-01 Imprint: 0698
Capsules, 200 mg (yellow); bottles of 500
NDC 0456-0698-02 Imprint: 0698

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Rev. 3/03 (04)

Mfd. by
Cardinal Health
St. Petersburg, Florida 33716
for
FOREST PHARMACEUTICALS, INC.
SUBSIDIARY OF FOREST LABORATORIES, INC.
ST. LOUIS, MISSOURI 63045

Shown in Product Identification Guide, page 312

[redacted]

: 8 Weeks After The End of Treatment

[illegible]ent Group [illegible] Patients Cured [illegible] of Patients)	Diff[illegible] OAC [illegible] (95% Confi[illegible])
10-day OAC	
81.6% (N=179)	[illegible]
72.3% (N=206)	[illegible]
10-day OAC	
81.6% (N=179)	[illegible]
73.3% (N=206)	[illegible]
10-day OAC	
81.6% (N=179)	[illegible]
73.3% (N=206)	[illegible]

[illegible] infection documented at baseline, defined as a [illegible] [illegible]tment. Patients who dropped out of the study [illegible] able analysis as failures of therapy.
[illegible]ated *H. pylori* infection at baseline as defined [illegible] [illegible]ded as failures of therapy
[illegible]tion rates for 7-day RAC minus 10-day RAC [illegible]

Pregnancy
Teratogenic Effects. Pregnancy Category [illegible] studies have been performed in rats at [illegible] to 30 mg/kg/day (plasma AUC of 13.8 [illegible] times the human exposure at the recom[illegible] (88.8D) and rabbits at intravenous doses up [illegible] (plasma AUC of 7.3 μg•hr/mL, about 8 times [illegible] posure at the recommended dose for GERD) [illegible] vealed no evidence of impaired fertility or [illegible] due to rabeprazole. There are, however, [illegible] well-controlled studies in pregnant women. [illegible] reproduction studies are not always predic[illegible] sponse, this drug should be used during pr[illegible] clearly needed.
Nursing Mothers
Following intravenous administration of [illegible] beprazole to lactating rats, radioactivity [illegible] levels that were 2- to 7-fold higher than le[illegible] It is not known if unmetabolized rabepraz[illegible] human breast milk. Administration of rabep[illegible] late gestation and during lactation at [illegible] day (about 195-times the human dose [illegible] sulted in decreases in body weight gain [illegible] many drugs are excreted in milk, and [illegible] tial for adverse reactions to nursing infant[illegible] azole, a decision should be made to [illegible] discontinue the drug, taking into account [illegible] the drug to the mother.
Pediatric Use
The safety and effectiveness of rabepraz[illegible] tients have not been established.
Use in Women
Duodenal ulcer and erosive esophagitis [illegible] women are similar to those in men. Adverse [illegible] oratory test abnormalities in women [illegible] lar to those in men.
Geriatric Use
Of the total number of subjects in [illegible] ACIPHEX®, 19% were 65 years and over [illegible] years and over. No overall differences in [illegible] ness were observed between these sub[illegible] subjects, and other reported clinical [illegible] identified differences in responses bet[illegible] younger patients, but greater sensitivity [illegible] viduals cannot be ruled out.

ADVERSE REACTIONS
Worldwide, over 2900 patients have be[illegible] beprazole in Phase II-III clinical trials [illegible] dosages and durations of treatment. In [illegible] treatment has been well-tolerated in [illegible] long-term trials. The adverse events [illegible] similar between the 10 and 20 mg do[illegible] Incidence in Controlled North American [illegible] ical Trials
In an analysis of adverse events [illegible] probably related to treatment appear[illegible] of ACIPHEX® patients and appear[illegible] quency than placebo in controlled N[illegible] region trials, the incidence of head[illegible] for ACIPHEX® versus 1.6% for [illegible] In short and long-term studies, the [illegible] events, regardless of causality were [illegible] treated patients. Rare events are [illegible] patients.
Body as a Whole: asthenia, fever, [illegible] malaise, chest pain substernal, and [illegible]

[illegible] edema, enlarged, face edema. Lymphatic [illegible] System: hypertension, myocardial in[illegible] [illegible] abnormal, migraine, syncope, an[illegible] [illegible] branch block, palpitation, sinus brady[illegible] Rare: bradycardia, pulmonary embolus, [illegible] tachycardia, thrombophlebitis, vasodila[illegible] [illegible] and ventricular tachycardia. Diges[illegible] [illegible] nausea, abdominal pain, vomiting, [illegible] constipation, dry mouth, eructation, [illegible] hemorrhage, melena, anorexia, chole[illegible] ulceration, stomatitis, dysphagia, gingi[illegible] increased appetite, abnormal stools, coli[illegible] [illegible] colitis, pancreatitis, proctitis. Rare: [illegible] cholangitis, duodenitis, gastrointestinal [illegible] encephalopathy, hepatitis, hepatoma, [illegible] salivary gland enlargement, thirst. En[illegible] [illegible] hyperthyroidism, hypothyroidism. Hemic & [illegible] anemia, ecchymosis, lymphadenopathy, [illegible] *Metabolic & Nutritional Disorders:* [illegible] edema, weight gain, gout, dehydration, [illegible] *Skeletal System:* myalgia, arthritis, [illegible] pain, arthrosis, bursitis. Rare: twitching. [illegible] insomnia, anxiety, dizziness, depression, [illegible] hypertonia, neuralgia, vertigo, [illegible] dreams, libido decreased, neuropathy, [illegible] Rare: agitation, amnesia, confusion, ex[illegible] [illegible] hyperkinesia. *Respiratory System:* [illegible] epistaxis, laryngitis, hiccup, hyperventil[illegible] hypoventilation. *Skin and Appendages:* [illegible] urticaria, alopecia. Rare: dry skin, [illegible] skin discoloration. *Special Senses:* [illegible] glaucoma, dry eyes, abnormal vision, [illegible] Rare: corneal opacity, blurry vision, [illegible] eye pain, retinal degeneration, strabis[illegible] [illegible] System: cystitis, urinary frequency, dys[illegible] kidney calculus, metrorrhagia, poly[illegible] enlargement, hematuria, impotence, [illegible] orchitis, urinary incontinence.
[illegible] The following changes in laboratory [illegible] reported as adverse events: abnormal [illegible] creatine phosphokinase increased, [illegible] hypercholesteremia, hyperglycemia, [illegible] hypokalemia, hyponatremia, leukocytosis, [illegible] function tests abnormal, prostatic specific [illegible] SGPT increased, urine abnormality, WBC [illegible]

[illegible] studies, 3/1456 (0.2%) patients treated [illegible] and 2/237 (0.8%) patients treated with pla[illegible] treatment-emergent abnormalities (which [illegible] study or present at study entry with an [illegible] baseline value) in SGOT (AST), SGPT [illegible] of the three rabeprazole patients expe[illegible] right upper quadrant pain, nausea or [illegible]

[illegible] with Amoxicillin and Clarithromycin [illegible] triple combination therapy with ra[illegible] amoxicillin and clarithromycin (RAC), no ad[illegible] in this drug combination were [illegible] particular study, the most frequently [illegible] adverse events for patients who re[illegible] for 3 or 10 days were diarrhea (8% and [illegible] (3% and 10%), respectively.
[illegible] laboratory abnormalities particular [illegible] were observed.
[illegible] on adverse events or laboratory [illegible] and clarithromycin, refer to their re[illegible] prescribing information, ADVERSE RE[illegible]

[illegible] Events: Additional adverse events [illegible] marketing experience with ra[illegible] sudden death, coma and hyperammo[illegible] rhabdomyolysis, disorientation and delir[illegible] [illegible]; bullous and other drug [illegible] dermatologic reactions includ[illegible] [illegible] (some fatal), Stevens-Johnson [illegible] epidermal necrolysis; interstitial pneumo[illegible] and TSH elevations. In most in[illegible] [illegible] to rabeprazole sodium was un[illegible] [illegible] leukocytosis, hemolytic anemia, [illegible] and thrombocytopenia have been [illegible] prothrombin time/INR in patients [illegible] warfarin have been reported.

[illegible] the management of overdose are [illegible] it is advisable to contact a Poison [illegible] the latest recommendations [illegible] overdose of any drug. There has [illegible] large overdose with rabeprazole. [illegible] overdosage with rabeprazole [illegible] maximum reported overdose was [illegible] signs or symptoms associated [illegible] Patients with Zollinger-Ellison [illegible] with up to 120 mg rabeprazole [illegible] rabeprazole is known. Rabepra[illegible] bound and is not readily dialyza[illegible] treatment should be sympto[illegible]

[illegible] rabeprazole at 786 mg/kg and [illegible] mice and rats, respectively. The [illegible] was not lethal to dogs. The [illegible] were hypoactivity, labored [illegible] position and convulsions in mice [illegible] tremor, convulsions and coma [illegible]

DOSAGE AND ADMINISTRATION
Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for four to eight weeks. (See INDICATIONS AND USAGE.) For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX® may be considered.
Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)
The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily. (See INDICATIONS AND USAGE.)
Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)
The recommended adult oral dose is one ACIPHEX® 20 mg delayed-release tablet to be taken once daily for 4 weeks. (See INDICATIONS AND USAGE.) If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered.
Healing of Duodenal Ulcers
The recommended adult oral dose is one ACIPHEX® 20 mg delayed release tablet to be taken once daily after the morning meal for a period up to four weeks. (See INDICATIONS AND USAGE.) Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.
Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
Three Drug Regimen*:

Aciphex	20 mg	Twice Daily for 7 Days
Amoxicillin	1000 mg	Twice Daily for 7 Days
Clarithromycin	500 mg	Twice Daily for 7 Days

All three medications should be taken twice daily with the morning and evening meals.

* It is important that patients comply with the full 7-day regimen. (See CLINICAL STUDIES section.)

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of ACIPHEX® in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX® for up to one year.
No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.
ACIPHEX® tablets should be swallowed whole. The tablets should not be chewed, crushed, or split. ACIPHEX® can be taken with or without food.

HOW SUPPLIED
ACIPHEX® 20 mg is supplied as delayed-release light yellow enteric-coated tablets. The name and strength, in mg, (ACIPHEX 20) is imprinted on one side.
Bottles of 30 (NDC 62856-243-30)
Bottles of 90 (NDC 62856-243-90)
Unit Dose Blisters Packages of 100 (10 × 10) (NDC 62856-243-41)
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.

REFERENCES
1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.

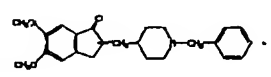
Rx only.
ACIPHEX® is a registered trademark of Eisai Co., Ltd., Tokyo, Japan.
Manufactured and Marketed by Eisai Inc., Teaneck, NJ 07666.
Marketed by Janssen Pharmaceutica Inc., Titusville, NJ 08560

Revised August 2003

Shown in Product Identification Guide, page 311

ARICEPT® ℞
[ă-ri'-sept]
(Donepezil Hydrochloride Tablets)

DESCRIPTION
ARICEPT® (donepezil hydrochloride) is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride. Donepezil hydrochloride is commonly referred to in the pharmacological literature as E2020. It has an empirical formula of $C_{24}H_{29}NO_3HCl$ and a molecular weight of 415.96. Donepezil hydrochloride is a white crystalline powder and is freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile and practically insoluble in ethyl acetate and in n-hexane.



ARICEPT® is available for oral administration in film-coated tablets containing 5 or 10 mg of donepezil hydrochloride. Inactive ingredients are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. The film coating contains talc, polyethylene glycol, hypromellose and titanium dioxide. Additionally, the 10 mg tablet contains yellow iron oxide (synthetic) as a coloring agent.

CLINICAL PHARMACOLOGY
Current theories on the pathogenesis of the cognitive signs and symptoms of Alzheimer's Disease attribute some of them to a deficiency of cholinergic neurotransmission.
Donepezil hydrochloride is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that donepezil alters the course of the underlying dementing process.
Clinical Trial Data
The effectiveness of ARICEPT® as a treatment for Alzheimer's Disease is demonstrated by the results of two randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's Disease (diagnosed by NINCDS and DSM III-R criteria, Mini-Mental State Examination ≥ 10 and ≤ 26 and Clinical Dementia Rating of 1 or 2). The mean age of patients participating in ARICEPT® trials was 73 years with a range of 50 to 94. Approximately 62% of patients were women and 38% were men. The racial distribution was white 95%, black 3% and other races 2%.
Study Outcome Measures: In each study, the effectiveness of treatment with ARICEPT® was evaluated using a dual outcome assessment strategy.
The ability of ARICEPT® to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.
The patients recruited as participants in each study had mean scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) of approximately 26 units, with a range from 4 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggest that they gain 6 to 12 units a year on the ADAS-cog. However, lesser degrees of change are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in ARICEPT® trials was approximately 2 to 4 units per year.
The ability of ARICEPT® to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC plus. The CIBIC plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC plus evaluations from other clinical trials. The CIBIC plus used in ARICEPT® trials was a semi-structured instrument that was intended to examine four major areas of patient function: General, Cognitive, Behavioral and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behavior of the patient over the interval rated. The CIBIC plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "markedly worse." The

Continued on next page

Aricept—Cont.

CIBIC plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Thirty-Week Study

In a study of 30 weeks duration, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of ARICEPT®. The 30-week study was divided into a 24-week double-blind active treatment phase followed by a 6-week single-blind placebo washout period. The study was designed to compare 5 mg/day or 10 mg/day fixed doses of ARICEPT® to placebo. However, to reduce the likelihood of cholinergic effects, the 10 mg/day treatment was started following an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 30 weeks of the study. After 24 weeks of treatment, the mean differences in the ADAS-cog change scores for ARICEPT® treated patients compared to the patients on placebo were 2.8 and 3.1 units for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. While the treatment effect size may appear to be slightly greater for the 10 mg/day treatment, there was no statistically significant difference between the two active treatments.

Following 6 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT® treatment groups were indistinguishable from those patients who had received only placebo for 30 weeks. This suggests that the beneficial effects of ARICEPT® abate over 6 weeks following discontinuation of treatment and do not represent a change in the underlying disease. There was no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy.

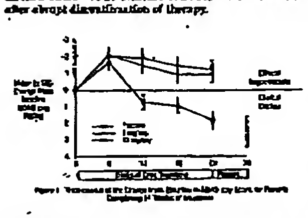


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment

Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to placebo and ARICEPT® have a wide range of responses, but that the active treatment groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo, respectively.

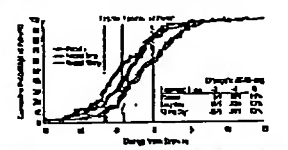


Figure 2. Cumulative Percentage of Patients Completing 24 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 80%, 5 mg/day 85%, and 10 mg/day 68%.

Effects on the CIBIC plus: Figure 3 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 24 weeks of treatment. The mean drug-placebo differences for these groups of patients were 0.35 units and 0.39 units for 5 mg/day and 10 mg/day of ARICEPT®, respectively. These differences were statistically significant. There was no statistically significant difference between the two active treatments.

[See figure at top of next column]

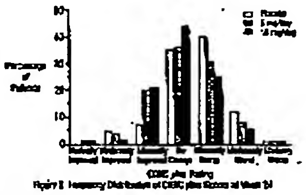


Figure 3. Frequency Distribution of CIBIC plus Scores at Week 24

Fifteen-Week Study

In a study of 15 weeks duration, patients were randomized to receive single daily doses of placebo or either 5 mg/day or 10 mg/day of ARICEPT® for 12 weeks, followed by a 3-week placebo washout period. As in the 30-week study, to avoid acute cholinergic effects, the 10 mg/day treatment followed an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-Cog: Figure 4 illustrates the time course of the change from baseline in ADAS-cog scores for all three dose groups over the 15 weeks of the study. After 12 weeks of treatment, the differences in mean ADAS-cog change scores for the ARICEPT® treated patients compared to the patients on placebo were 2.7 and 3.0 units each, for the 5 and 10 mg/day ARICEPT® treatment groups respectively. These differences were statistically significant. The effect size for the 10 mg/day group may appear to be slightly larger than that for 5 mg/day. However, the differences between active treatments were not statistically significant.

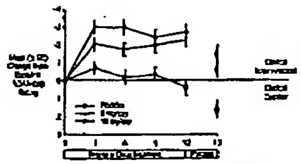


Figure 4. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing the 15-week Study

Following 3 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT® treatment groups increased, indicating that discontinuation of ARICEPT® resulted in a loss of its treatment effect. The duration of this placebo washout period was not sufficient to characterize the rate of loss of the treatment effect, but, the 30-week study (see above) demonstrated that treatment effects associated with the use of ARICEPT® abate within 6 weeks of treatment discontinuation.

Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who attained the measure of improvement in ADAS-cog score shown on the X axis. The same three change scores, (7-point and 4-point reductions from baseline or no change in score) as selected for the 30-week study have been used for this illustration. The percentages of patients achieving those results are shown in the inset table.

As observed in the 30-week study, the curves demonstrate that patients assigned to either placebo or to ARICEPT® have a wide range of responses, but that the ARICEPT® treated patients are more likely to show the greater improvements in cognitive performance.

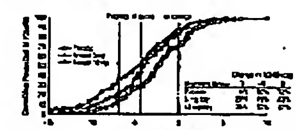


Figure 5. Cumulative Percentage of Patients with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients Within Each Treatment Group Who Completed the Study Were: Placebo 93%, 5 mg/day 90%, and 10 mg/day 82%.

Effects on the CIBIC plus: Figure 6 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 12 weeks of treatment. The differences in mean scores for ARICEPT® treated patients compared to the patients on placebo at Week 12 were 0.36 and 0.38 units for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences were statistically significant.

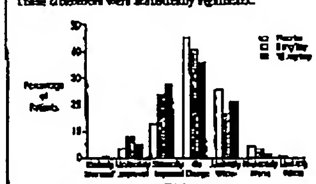


Figure 6. Frequency Distribution of CIBIC plus Scores at Week 12

In both studies, patient age, sex and race were not found to predict the clinical outcome of ARICEPT® treatment.

Clinical Pharmacokinetics

Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily. Neither food nor time of administration (morning vs. evening dose) influence [illegible] rate of absorption. The elimination half life [illegible] about 70 hours and the mean apparent [illegible] (Cl/F) is 0.13 L/hr/kg. Following multiple [illegible] tion, donepezil accumulates in plasma [illegible] steady state is reached within 15 days. The [illegible] ume of distribution is 12 L/kg. Donepezil [illegible] 96% bound to human plasma proteins, [illegible] (about 75%) and alpha$_1$ - acid glycoprotein [illegible] the concentration range of 2-1000 ng/mL. [illegible] Donepezil is both excreted in the urine [illegible] sively metabolized to four major metabolites [illegible] are known to be active, and a number of [illegible] not all of which have been identified. [illegible] lized by CYP 450 isoenzymes 2D6 and [illegible] glucuronidation. Following administration [illegible] donepezil, plasma radioactivity, expressed [illegible] the administered dose, was present [illegible] donepezil (53%) and as 6-O-desmethyl [illegible] which has been reported to inhibit AChE [illegible] as donepezil in vitro and was found in [illegible] tions equal to about 20% of donepezil. [illegible] and 15% of the total radioactivity was [illegible] and feces, respectively, over a period of [illegible] remained unrecovered, with about 17% [illegible] dose recovered in the urine as unchanged [illegible]

Special Populations:

Hepatic Disease: In a study of 10 patients [illegible] coholic cirrhosis, the clearance of ARICEPT® [illegible] by 20% relative to 10 healthy age and sex [illegible]

Renal Disease: In a study of 11 patients [illegible] severe renal impairment (Cl_{cr} < 18 mL [illegible] clearance of ARICEPT® did not differ from [illegible] matched healthy subjects.

Age: No formal pharmacokinetic study [illegible] examine age related differences in the [illegible] ARICEPT®. However, mean plasma ARICEPT® [illegible] tions measured during therapeutic drug [illegible] derly patients with Alzheimer's Disease [illegible] those observed in young healthy volunteers.

Gender and Race: No specific pharmacokinetic [illegible] conducted to investigate the effects of [illegible] the disposition of ARICEPT®. However, [illegible] macokinetic analyses indicates that gender [illegible] race and Caucasian) did not affect [illegible] ARICEPT®.

Drug-Drug Interactions

Drugs Highly Bound to Plasma Proteins [illegible] ment studies have been performed in [illegible] highly bound drug (96%) and other drugs [illegible] line, digoxin, and warfarin. ARICEPT® [illegible] 0.3-10 µg/mL did not affect the binding [illegible] (5 µg/mL), digoxin (2 ng/mL), and warfarin [illegible] man albumin. Similarly, the binding of [illegible] man albumin was not affected by [illegible] warfarin.

Effect of ARICEPT® on the Metabolism [illegible] No in vivo clinical trials have investigated [illegible] ARICEPT® on the clearance of drugs [illegible] 3A4 (e.g. cisapride, terfenadine) or by [illegible] mazine). However, in vitro studies show [illegible] ing to these enzymes (mean K_i about [illegible] given the therapeutic plasma concentrations [illegible] (164 nM), indicates little likelihood of [illegible] Whether ARICEPT® has any potential [illegible] tion is not known.

Formal pharmacokinetic studies evaluated [illegible] ARICEPT® for interaction with theophylline, [illegible] warfarin, digoxin and ketoconazole. [illegible] ARICEPT® on the pharmacokinetics [illegible] observed.

Effect of Other Drugs on the Metabolism [illegible] Ketoconazole and quinidine, inhibitors [illegible] and 2D6, respectively, inhibit donepezil [illegible] Whether there is a clinical effect of [illegible] In a 7 day crossover study in 18 healthy [illegible] conazole (200 mg q.d.) increased mean [illegible] concentrations (AUC_{0-24} and C_{max}) by [illegible] evance of this increase in concentration [illegible] Inducers of CYP 2D6 and CYP 3A4 (e.g. [illegible] mazepine, dexamethasone, rifampin [illegible] could increase the rate of elimination [illegible] Formal pharmacokinetic studies [illegible] metabolism of ARICEPT® is not [illegible] concurrent administration of digoxin [illegible]

INDICATIONS AND USAGE

ARICEPT® is indicated for the treatment [illegible] ate dementia of the Alzheimer's type [illegible]

CONTRAINDICATIONS

ARICEPT® is contraindicated in [illegible] persensitivity to donepezil hydrochloride [illegible] derivatives.

WARNINGS

Anesthesia: ARICEPT®, as a cholinesterase inhibitor, is [illegible] likely to exaggerate succinylcholine-type [illegible] during anesthesia.

Cardiovascular Conditions: Because [illegible] ical action, cholinesterase inhibitors [illegible] fects on the sinoatrial and atrioventricular [illegible] fect may manifest as bradycardia or [illegible] both with and without known [illegible] [illegible] Syncopal episodes have been reported in [illegible] the use of ARICEPT®.

[illegible] *Conditions:* Through their primary action, [illegible] inhibitors may be expected to increase [illegible] tion due to increased cholinergic activity. [illegible] should be monitored closely for symp- [illegible] occult gastrointestinal bleeding, especially [illegible] risk for developing ulcers, e.g., those with [illegible] disease or those receiving concurrent non- [illegible] inflammatory drugs (NSAIDS). Clinical stud- [illegible] have shown no increase, relative to pla- [illegible] dence of either peptic ulcer disease or [illegible] bleeding.

[illegible] predictable consequence of its pharmaco- [illegible] has been shown to produce diarrhea, nau- [illegible] These effects, when they occur, appear [illegible] with the 10 mg/day dose than with the [illegible] In most cases, these effects have been mild [illegible] sometimes lasting one to three weeks, and [illegible] during continued use of ARICEPT®.

[illegible] Although not observed in clinical trials of [illegible] cholinomimetics may cause bladder outflow [illegible]

[illegible] *Seizures:* Cholinomimetics are [illegible] have potential to cause generalized convul- [illegible] seizure activity also may be a manifestation [illegible]

[illegible] Because of their cholinomimetic [illegible] inhibitors should be prescribed with [illegible] with a history of asthma or obstructive [illegible]

[illegible] (See Clinical Pharmacology, Clinical [illegible] Drug-drug Interactions)

[illegible] *on the Metabolism of Other Drugs:* [illegible] trials have investigated the effect of [illegible] clearance of drugs metabolized by CYP [illegible] terfenadine) or by CYP 2D6 (e.g. imip- [illegible] in vitro studies show a low rate of bind- [illegible] (mean K_i about 50-130 µM), that, [illegible] plasma concentrations of donepezil [illegible] little likelihood of interference.

[illegible] has any potential for enzyme induc- [illegible]

[illegible] studies evaluated the potential of [illegible] with theophylline, cimetidine, [illegible] and ketoconazole. No effects of [illegible] pharmacokinetics of these drugs were [illegible]

[illegible] on the Metabolism of ARICEPT®: [illegible] quinidine, inhibitors of CYP450, 3A4 [illegible] inhibit donepezil metabolism in vitro. [illegible] clinical effect of quinidine is not known. [illegible] study in 18 healthy volunteers, keto- [illegible] increased mean donepezil (5mg q.d.) [illegible] and C_{max}) by 36%. The clinical rel- [illegible] in concentration is unknown. [illegible] and CYP 3A4 (e.g., phenytoin, carba- [illegible] rifampin, and phenobarbital) [illegible] of elimination of ARICEPT®. [illegible] studies demonstrated that the me- [illegible] is not significantly affected by con- [illegible] of digoxin or cimetidine.

[illegible] Because of their mechanism of [illegible] inhibitors have the potential to inter- [illegible] anticholinergic medications. [illegible] and Other Cholinesterase Inhibi- [illegible] may be expected when cholines- [illegible] given concurrently with succinylcho- [illegible] blocking agents or cholinergic [illegible]

[illegible] Impairment of Fertility — [illegible] potential was obtained in an [illegible] study of donepezil hydrochloride [illegible] at doses up to 180 mg/kg/day (ap- [illegible] the maximum recommended human [illegible] or in a 104-week carcinogenicity [illegible] at doses up to 30 mg/kg/day [illegible] the maximum recommended [illegible] basis).

[illegible] in the Ames reverse mutation [illegible] mouse lymphoma forward muta- [illegible] chromosome aberration test. In [illegible] lung (CHL) cells, some clasto- [illegible] Donepezil was not clastogenic [illegible] micronucleus test and was not geno- [illegible] DNA synthesis assay in rats. [illegible] fertility in rats at doses up to [illegible] 8 times the maximum recom- [illegible] basis).

[illegible] teratology studies conducted in [illegible] to 16 mg/kg/day (approximately [illegible] recommended human dose on [illegible] rabbits at doses up to 10 mg/ [illegible] times the maximum recom- [illegible] basis) did not disclose any [illegible] potential of donepezil. However, [illegible] rats were given up to 10 mg/ [illegible] the maximum recommended [illegible] from day 17 of gestation [illegible] there was a slight increase in [illegible] in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children.

Geriatric Use

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical studies with ARICEPT® was 73 years; 80% of these patients were between 65 and 84 years old and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥ 65 years old and < 65 years old.

ADVERSE REACTIONS

Adverse Events Leading to Discontinuation

The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/% Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT®

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of rates of adverse events in patients titrated to 10 mg/day over 1 and 6 weeks

	No titration		One week titration	Six week titration
Adverse Event	Placebo (n=315)	5 mg/day (n=311)	10 mg/day (n=315)	10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in [illegible]

The events cited reflect expe[illegible] monitored conditions of clinic[illegible] patient population. In actual [illegible] clinical trials, these frequency [illegible] the conditions of use, reportin[illegible] patients treated may differ. T[illegible] gest signs and symptoms that [illegible] of patients in placebo-cont[illegible] ARICEPT® and for which [illegible] greater for ARICEPT® assign[illegible] tients. In general, adverse eve[illegible] in female patients and with a[illegible]

Table 3. Adverse Events Rep[illegible] Trials in at Least 2% of Pati[illegible] and at a Higher Frequency th[illegible]

Body System/Adverse Event	[illegible]
Percent of Patients with any Adverse Event	[illegible]
Body as a Whole	
Headache	[illegible]
Pain, various locations	[illegible]
Accident	[illegible]
Fatigue	[illegible]
Cardiovascular System	
Syncope	[illegible]
Digestive System	
Nausea	[illegible]
Diarrhea	[illegible]
Vomiting	[illegible]
Anorexia	[illegible]
Hemic and Lymphatic System	
Ecchymosis	[illegible]
Metabolic and Nutritional Syst[illegible]	
Weight Decrease	[illegible]
Musculoskeletal System	
Muscle Cramps	[illegible]
Arthritis	[illegible]
Nervous System	
Insomnia	[illegible]
Dizziness	[illegible]
Depression	[illegible]
Abnormal Dreams	[illegible]
Somnolence	[illegible]
Urogenital System	
Frequent Urination	[illegible]

Other Adverse Events Observe[illegible]

ARICEPT® has been administere[illegible] during clinical trials worldwid[illegible] these patients have been treated [illegible] more than 1000 patients have b[illegible] months. Controlled and uncontr[illegible] States included approximately [illegible] the highest dose of 10 mg/day, th[illegible] patients treated for 3 months, 4[illegible] months and 116 patients treated [illegible] of patient exposure is from 1 to 1[illegible] Treatment emergent signs and [illegible] during 3 controlled clinical trials [illegible] in the United States were recorde[illegible] clinical investigators using termi[illegible] ing. To provide an overall estimat[illegible] dividuals having similar types of [illegible] grouped into a smaller number o[illegible] using a modified COSTART dicti[illegible] cies were calculated across all stu[illegible] used in the listing below. The frequ[illegible] portion of 900 patients from thes[illegible] that event while receiving ARICE[illegible] occurring at least twice are inclu[illegible]

Con[illegible]

[illegible] Syncopal episodes have been reported in association with the use of ARICEPT®.

[illegible] Conditions: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

[illegible] a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®.

[illegible] Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction.

[illegible] Conditions: Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease.

[illegible] Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

[illegible]

[illegible] Interactions (see Clinical Pharmacology: Clinical Pharmacokinetics: Drug-drug Interactions)

Effect of ARICEPT® on the Metabolism of Other Drugs

No in vivo clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine). However, in vitro studies show a low rate of binding to these enzymes (mean Ki about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether ARICEPT® has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential of ARICEPT® for interaction with theophylline, cimetidine, warfarin, digoxin and ketoconazole. No effects of ARICEPT® on the pharmacokinetics of these drugs were observed.

Effect of Other Drugs on the Metabolism of ARICEPT®

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism in vitro. Whether there is a clinical effect of quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations (AUC_{0-24} and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown.

Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®.

Pharmacokinetic studies demonstrated that the metabolism of ARICEPT® is not significantly affected by concurrent administration of digoxin or cimetidine.

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose on a mg/m² basis), or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m² basis).

Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay in vitro. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the in vivo mouse micronucleus test and was not genotoxic in an in vivo unscheduled DNA synthesis assay in rats.

Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis).

Pregnancy Category C: Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential of donepezil. However, when pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and [illegible]

day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children.

Geriatric Use

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical studies with ARICEPT® was 73 years; 80% of these patients were between 65 and 84 years old and 49% of patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥ 65 years old and < 65 years old.

ADVERSE REACTIONS

Adverse Events Leading to Discontinuation

The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/% Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT®

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of rates of adverse events in patients titrated to 10 mg/day over 1 and 6 weeks

	No titration		One week titration	Six week titration
Adverse Event	Placebo (n=315)	5 mg/day (n=311)	10 mg/day (n=315)	10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramp	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials

The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients with any Adverse Event	72	74
Body as a Whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		
Frequent Urination	1	2

Other Adverse Events Observed During Clinical Trials

ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days.

Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those al-

[redacted]

rarely listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States.

Body as a Whole: *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness.

Cardiovascular System: *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis.

Digestive System: *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

Endocrine System: *Infrequent:* diabetes mellitus, goiter.

Hemic and Lymphatic System: *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Metabolic and Nutritional Disorders: *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal System: *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation.

Nervous System: *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing.

Respiratory System: *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and Appendages: *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer.

Special Senses: *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital System: *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature.

DOSAGE AND ADMINISTRATION

The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day.

The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference.

Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks.

ARICEPT® should be taken in the evening, just prior to retiring. ARICEPT® can be taken with or without food.

HOW SUPPLIED

ARICEPT® is supplied as film-coated, round tablets containing either 5 mg or 10 mg of donepezil hydrochloride.

The 5 mg tablets are white. The strength, in mg (5), is debossed on one side and ARICEPT is debossed on the other side.

The 10 mg tablets are yellow. The strength, in mg (10), is debossed on one side and ARICEPT is debossed on the other side.

5 mg (White)	Bottles of 30 (NDC# 62856-245-30)
	Bottles of 90 (NDC# 62856-245-90)
	Unit Dose Blister Package 100 (10x10)
	(NDC# 62856-245-41)
10 mg (Yellow)	Bottles of 30 (NDC# 62856-246-30)
	Bottles of 90 (NDC# 62856-246-90)
	Unit Dose Blister Package 100 (10x10)
	(NDC# 62856-246-41)

Storage: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F).

℞ only

Manufactured and Marketed by Eisai Inc., Teaneck, NJ 07666
Marketed by
Pfizer Inc, New York, NY 10017

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203335 Revised April 2004

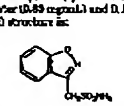
Shown in Product Identification Guide, page 311

ZONEGRAN® ℞

[zōn' e grăn]
(zonisamide)
Capsules
℞ only

DESCRIPTION

ZONEGRAN® (zonisamide) is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents. The active ingredient is zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. The empirical formula is $C_8H_8N_2O_3S$ with a molecular weight of 212.23. Zonisamide is a white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL). The chemical structure is:



ZONEGRAN is supplied for oral administration as capsules containing 25 mg, 50 mg or 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

CLINICAL PHARMACOLOGY

Mechanism of Action: The precise mechanism(s) by which zonisamide exerts its antiseizure effect is unknown. Zonisamide demonstrated anticonvulsant activity in several experimental models. In animals, zonisamide was effective against tonic extension seizures induced by maximal electroshock but ineffective against clonic seizures induced by subcutaneous pentylenetetrazol. Zonisamide raised the threshold for generalized seizures in the kindled rat model and reduced the duration of cortical focal seizures induced by electrical stimulation of the visual cortex in cats. Furthermore, zonisamide suppressed both [illegible] the secondarily generalized seizures, [illegible] application of tungstic acid gel to rat co[illegible] in cats. The relevance of these models to [illegible] unknown.

Zonisamide may produce these effects th[illegible] dium and calcium channels. In vitro pha[illegible] ies suggest that zonisamide blocks sodiu[illegible] duces voltage-dependent, transient inwa[illegible] Ca^{2+} currents), consequently stabilizing [illegible] branes and suppressing neuronal hypers[illegible] vitro binding studies have demonstrated [illegible] binds to the GABA/benzodiazepine recep[illegible] plex in an allosteric fashion which does [illegible] in chloride flux. Other in vitro studies [illegible] that zonisamide (10–30 µg/mL) suppr[illegible] driven electrical activity without affect[illegible] GABA or glutamate responses (cultured [illegible] neurons) or neuronal or glial uptake of [illegible] presynaptic terms). Thus, zonisamide does [illegible] tentiate the synaptic activity of GABA. In [illegible] studies demonstrated that zonisamide [illegible] dopaminergic and serotonergic [illegible] Zonisamide also has weak carbonic anh[illegible] tivity, but this pharmacologic effect is [illegible] major contributing factor in the anti[illegible] zonisamide.

Pharmacokinetics: Following a [illegible] zonisamide dose, peak plasma conc[illegible] 2–5 µg/mL) in normal volunteers occur [illegible] the presence of food, the time to maxim[illegible] delayed, occurring at 4–6 hours, but fo[illegible] the bioavailability of zonisamide. Zon[illegible] binds to erythrocytes, resulting in an ei[illegible] centration of zonisamide in red blood [illegible] plasma. The pharmacokinetics of zoni[illegible] performed in the range of 200–400 mg, bu[illegible] increase disproportionately at 800 mg, p[illegible] urable binding of zonisamide to RBC. O[illegible] reached, steady state is achieved within [illegible] ination half-life of zonisamide in plasm[illegible] The elimination half-life of zonisamide [illegible] mately 105 hours.

The apparent volume of distribution (V/F) [illegible] about 1.45 L/kg following a 400 mg oral [illegible] concentrations of 1.0–7.0 µg/mL, [illegible] bound to human plasma protein. [illegible] zonisamide is unaffected in the presence [illegible] centrations of phenytoin, phenobarbital [illegible]

Metabolism and Excretion: Following [illegible] of ^{14}C-zonisamide to healthy volunteer[illegible] was detected in plasma. Zonisamide is e[illegible] urine as parent drug and as the glucuro[illegible] Following multiple dosing, 62% of the [illegible] ered in the urine, with 3% in the [illegible] Zonisamide undergoes acetylation to fo[illegible] mide and reduction to form the open ri[illegible] (sulfamoylacetyl phenol (SMAP)). Of the ex[illegible] recovered as zonisamide, 15% as N-[illegible] 50% as the glucuronide of SMAP. Red[illegible] to SMAP is mediated by cytochrom[illegible] (CYP3A4). Zonisamide does not induce [illegible]

Plasma clearance of zonisamide is [illegible] 0.30 mL/min/kg in patients not rece[illegible] antiepilepsy drugs (AEDs). The clear[illegible] increased to 0.5 mL/min/kg in patien[illegible] zyme-inducing AEDs.

Renal clearance is about 3.5 mL/min. [illegible] oral dose of zonisamide from RBC is [illegible]

Special Populations:

Renal Insufficiency: Single 300 m[illegible] were administered to three groups of [illegible] was a healthy group with a creatinin[illegible] from 70–152 mL/min. Group 2 and [illegible] nine clearance ranging from 14.5–[illegible] 20 mL/min, respectively. Zonisamid[illegible] creased with decreasing renal fun[illegible] 2.23 mL/min, respectively). Marke[illegible] creatinine clearance < 20 mL/min [illegible] an increase in zonisamide AUC of [illegible] AND ADMINISTRATION section).

Hepatic Disease: The pharmacok[illegible] in patients with impaired liver fu[illegible] studied (see DOSAGE AND AD[illegible] section).

Age: The pharmacokinetics of a 3[illegible] zonisamide was similar in young (m[illegible] elderly subjects (mean age 69 year[illegible]

Gender and Race: Information [illegible] and race on the pharmacokinetic[illegible] available.

Interactions of Zonisamide with [illegible] Drugs (AEDs): Concurrent med[illegible] either induce or inhibit CYP3A4 [illegible] trations of zonisamide. Concom[illegible] phenytoin and carbamazepine [illegible] plasma clearance from 0.30–0.[illegible] 0.5 mL/min/kg. The half-life [illegible] 27 hours by phenytoin, to 38 hour[illegible] carbamazepine, and to 46 hour[illegible] protein binding of phenytoin and [illegible] affected by zonisamide adminis[illegible] TIONS, Drug Interactions subs[illegible]

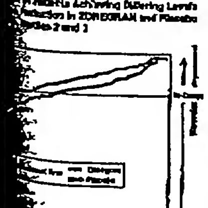
[illegible] The effectiveness of ZONEGRAN as adjunctive therapy (added to other antiepilepsy drugs) has [illegible] in three multicenter, placebo-controlled, [illegible] clinical trials (two domestic, one European) in patients with refractory partial onset seizures with or without secondary generalization. Each patient [illegible] of at least four partial onset seizures per [illegible] receiving one or two antiepilepsy drugs at [illegible] concentrations. The 499 patients (209 women, [illegible] in age from 13–68 years with a mean age [illegible] In the two US studies, over 80% of patients [illegible]; 100% of patients in the European [illegible] ZONEGRAN or placebo was added [illegible] therapy. The primary measure of effectiveness [illegible] percent reduction from baseline in partial [illegible] The secondary measure was proportion of [illegible] a 50% or greater seizure reduction from [illegible] The results described below are for [illegible] in the intent-to-treat populations.

[illegible] (n = 203), all patients had a 1-month baseline period, then received placebo or [illegible] one of two dose escalation regimens; either [illegible] five weeks, 200 mg/day for one week, [illegible] week, and then 400 mg/day for five [illegible] mg/day for one week, followed by 200 mg/ [illegible] then 300 mg/day for one week, then [illegible] weeks. This design allowed a 100 mg vs. [illegible] over weeks 1–5, and a 200 mg vs. placebo [illegible] weeks 2–5; the primary comparison [illegible] escalation groups combined) vs. placebo [illegible] The total daily dose was given as twice a [illegible] statistically significant treatment differences [illegible] ZONEGRAN were seen for doses of 100, 200, and [illegible]

[illegible] (n = 152) and third (n = 138) studies, patients [illegible] baseline, then were randomly assigned to [illegible] ZONEGRAN for three months. ZONEGRAN was [illegible] 100 mg/day for the first week, [illegible] second week, then 400 mg/day for two [illegible] the dose (ZONEGRAN or placebo) could [illegible] necessary to a maximum dose of 20 mg/kg/ [illegible] plasma level of 40 µg/mL. In the second [illegible] daily dose was given as twice a day dosing; [illegible] it was given as a single daily dose. The [illegible] average doses received in the studies [illegible] mg/day in the second and third studies, [illegible] studies demonstrated statistically significant [illegible] favoring ZONEGRAN for doses of 400– [illegible] There was no apparent difference between [illegible] twice daily dosing (in different studies). [illegible] (first 4 weeks) during titration demonstrated [illegible] statistically significant differences favoring [illegible] between 100 and 400 mg/day. The primary [illegible] both trials was for any dose over Weeks [illegible]

[illegible] proportion of patients (X-axis) whose [illegible] from baseline in the all partial seizure [illegible] greater than that indicated on the Y-axis in [illegible] placebo-controlled trials. A positive [illegible] indicates an improvement from baseline [illegible] seizure rate), while a negative value indicates [illegible] from baseline (i.e., an increase in seizure rate). [illegible] a display of this type, the curve for an [illegible] is shifted to the left of the curve for placebo. [illegible] of patients achieving any particular [illegible] seizure rate was consistently higher for [illegible] groups compared to the placebo groups. [illegible] indicates that approximately 25% of [illegible] ZONEGRAN experienced a 75% or [illegible] compared to approximately 10% in the [illegible]

[illegible] % Patients Achieving Differing Levels [illegible] Reduction in ZONEGRAN and Placebo [illegible] Studies 2 and 3



[illegible] % of Patients

[illegible] based on age, sex or race, as com[illegible] frequency from baseline, were [illegible]

[illegible]AGE

[illegible] adjunctive therapy in the treatment of [illegible] adults with epilepsy.

Table 1. Median % Reduction in All Partial Seizures and % Responders in Primary Efficacy Analyses: Intent-To[illegible] Analysis

Study	Median % reduction in partial seizures: ZONEGRAN	Median % reduction in partial seizures: Placebo	% Responders: ZONEGRAN	% Responders: Placebo
Study 1: Weeks 8–12:	n=98 40.5%*	n=72 9.0%	n=98 41.8%*	n=72 22.2%
Study 2: Weeks 8–12:	n=69 29.6%*	n=72 -3.2%	n=69 29.0%	n=72 15.0%
Study 3: Weeks 5–12:	n=67 27.2%*	n=66 -1.1%	n=67 28.2%*	n=66 12.0%

*p<0.05 compared to placebo

Table 2. Median % Reduction in All Partial Seizures and % Responders for Dose Analyses in Study 1: Intent-To[illegible] Analysis

Dose Group	Median % reduction in partial seizures: ZONEGRAN	Median % reduction in partial seizures: Placebo	% Responders: ZONEGRAN	% Responders: Placebo
100–400 mg/day: Weeks 8–12:	n=112 32.3%*	n=83 5.6%	n=112 32.1%*	n=83 9.6%
100 mg/day: Weeks 1–5:	n=56 24.7%*	n=80 8.3%	n=56 25.0%*	n=80 11.3%
200 mg/day: Weeks 2–5:	n=55 20.4%*	n=82 4.0%	n=55 25.5%*	n=82 9.8%

*p<0.05 compared to placebo

CONTRAINDICATIONS

ZONEGRAN is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

WARNINGS

Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately. Specific experience with sulfonamide type adverse reaction to zonisamide is described below.

Serious Skin Reactions: Consideration should be given to discontinuing ZONEGRAN in patients who develop an otherwise unexplained rash. If the drug is not discontinued, patients should be observed frequently. Seven deaths from severe rash (i.e. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) were reported in the first 11 years of marketing in Japan. All of the patients were receiving other drugs in addition to zonisamide. In post-marketing experience from Japan, a total of 49 cases of SJS or TEN have been reported, a reporting rate of 46 per million patient-years of exposure. Although this rate is greater than background, it is probably an underestimate of the true incidence because of under-reporting. There were no confirmed cases of SJS or TEN in the US, European, or Japanese development programs.

In the US and European randomized controlled trials, 6 of 269 (2.2%) zonisamide patients discontinued treatment because of rash compared to none on placebo. Across all trials during the US and European development, rash that led to discontinuation of zonisamide was reported in 1.4% of patients (12.0 events per 1000 patient-years of exposure). During Japanese development, serious rash or rash that led to study drug discontinuation was reported in 2.0% of patients (27.8 events per 1000 patient-years). Rash usually occurred early in treatment, with 85% reported within 16 weeks in the US and European studies and 90% reported within two weeks in the Japanese studies. There was no apparent relationship of dose to the occurrence of rash.

Serious Hematologic Events: Two confirmed cases of aplastic anemia and one confirmed case of agranulocytosis were reported in the first 11 years of marketing in Japan, rates greater than generally accepted background rates. There were no cases of aplastic anemia and two confirmed cases of agranulocytosis in the US, European, or Japanese development programs. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Oligohidrosis and Hyperthermia in Pediatric Patients: Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.

During the pre-approval development program in Japan, one case of oligohidrosis was reported in 403 pediatric patients, an incidence of 1 case per 285 patient-years of exposure. While there were no cases reported in the US or European development programs, fewer than 100 pediatric patients participated in these trials.

In the first 11 years of marketing in Japan, 38 cases were reported, an estimated reporting rate of about 1 case per 10,000 patient-years of exposure. In the first year of marketing in the US, 2 cases were reported, an estimated reporting rate of about 12 cases per 10,000 patient-years of exposure. These rates are underestimates of the true incidence because of under-reporting. There has also been one report of heat stroke in an 18-year-old patient in the US. Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was [illegible] in some cases. There have been no reported d[illegible] Pediatric patients appear to be at an increased r[illegible] zonisamide-associated oligohidrosis and hypertherm[illegible] Patients, especially pediatric patients, treated with Zo[illegible] should be monitored closely for evidence of dec[illegible] sweating and increased body temperature, especi[illegible] warm or hot weather. Caution should be used [illegible] zonisamide is prescribed with other drugs that predi[illegible] patients to heat-related disorders; these drugs includ[illegible] are not limited to, carbonic anhydrase inhibitors and [illegible] with anticholinergic activity.

The practitioner should be aware that the safety and [illegible] effectiveness of zonisamide in pediatric patients have not [illegible] established, and that zonisamide is not approved for u[illegible] pediatric patients.

Seizures on Withdrawal: As with other AEDs, a[illegible] withdrawal of ZONEGRAN in patients with epilepsy [illegible] precipitate increased seizure frequency or status epi[illegible] cus. Dose reduction or discontinuation of zonisamide s[illegible] be done gradually.

Teratogenicity: Women of child bearing potential wh[illegible] given zonisamide should be advised to use effective co[illegible] ception. Zonisamide was teratogenic in mice, rats, and [illegible] and embryolethal in monkeys when administered d[illegible] the period of organogenesis. A variety of fetal abnorm[illegible] including cardiovascular defects, and embryo-fetal de[illegible] occurred at maternal plasma levels similar to or lower [illegible] therapeutic levels in humans. These findings suggest [illegible] the use of ZONEGRAN during pregnancy in humans [illegible] present a significant risk to the fetus (see PRECAUTIO[illegible] Pregnancy subsection). It cannot be said with any c[illegible] dence, however, that even mild seizures do not pose a [illegible] hazards to the developing fetus. Zonisamide should be [illegible] during pregnancy only if the potential benefit justifies [illegible] potential risk to the fetus.

Cognitive/Neuropsychiatric Adverse Events: Use [illegible] ZONEGRAN was frequently associated with central [illegible] vous system-related adverse events. The most significan[illegible] these can be classified into three general categories: [illegible] psychiatric symptoms, including depression and psycho[illegible] 2) psychomotor slowing, difficulty with concentration, [illegible] speech or language problems, in particular, word-find[illegible] difficulties, and 3) somnolence or fatigue.

In placebo-controlled trials, 2.2% of patients discontinu[illegible] ZONEGRAN or were hospitalized for depression compa[illegible] to 0.4% of placebo patients, while 1.1% of ZONEGRAN [illegible] 0.4% of placebo patients attempted suicide. Among all [illegible] lepsy patients treated with ZONEGRAN, 1.4% were disc[illegible] tinued and 1.0% were hospitalized because of reported [illegible] pression or suicide attempts. In placebo-controlled tri[illegible] 2.2% of patients discontinued ZONEGRAN or were hos[illegible] talized due to psychosis or psychosis-related symptoms co[illegible] pared to none of the placebo patients. Among all epile[illegible] patients treated with ZONEGRAN, 0.9% were discontin[illegible] and 1.4% were hospitalized because of reported psychosis-[illegible] related symptoms.

Psychomotor slowing and difficulty with concentrati[illegible] occurred in the first month of treatment and were asso[illegible] ated with doses above 300 mg/day. Speech and langua[illegible] problems tended to occur after 6–10 weeks of treatment a[illegible] at doses above 300 mg/day. Although in most cases the [illegible] events were of mild to moderate severity, they at times l[illegible] to withdrawal from treatment.

Somnolence and fatigue were frequently reported CNS [illegible] verse events during clinical trials with ZONEGRAN. A[illegible] though in most cases these events were of mild to modera[illegible] severity, they led to withdrawal from treatment in 0.2%[illegible] the patients enrolled in controlled trials. Somnolence an[illegible]

Elidel—Cont.

topical corticosteroid, 42% of Elidel patients and 62% of vehicle patients used corticosteroids during the study. Corticosteroids were used for more than 7 days by 24% of Elidel patients and 54% of vehicle patients. An increased incidence of impetigo, skin infection, superinfection (infected atopic dermatitis), rhinitis, and urticaria were found in the patients that had used Elidel Cream and topical corticosteroid sequentially as compared to Elidel Cream alone.

In 3 randomized, double-blind vehicle-controlled pediatric studies and one active-controlled adult study, 843 and 328 patients respectively, were treated with Elidel Cream. In these clinical trials, 48 (4%) of the 1171 Elidel patients and 13 (3%) of 408 vehicle-treated patients discontinued therapy due to adverse events. Discontinuations [illegible] primarily due to application site reactions [illegible] infections. The most common application [illegible] application site burning, which occurred [illegible] patients treated with Elidel Cream.

The following table depicts the incidence of [illegible] pooled across the 2 identically designed [illegible] their open label extensions and the 1-year [illegible] pediatric patients ages 2-17. Data from the [illegible] controlled study is also included in this [illegible] events are listed regardless of relationship [illegible] (See table below)

Treatment Emergent Adverse Events (≥ 1%) in Elidel® Treatment Groups

	Pediatric Patients* Vehicle-Controlled (6 weeks) Elidel® Cream (N=267) N (%)	Pediatric Patients* Vehicle-Controlled (6 weeks) Vehicle (N=136) N (%)	Pediatric Patients* Open-Label (20 weeks) Elidel® Cream (N=335) N (%)	Pediatric Patients* Vehicle-Controlled (1 year) Elidel® Cream (N=272) N (%)	Pediatric Patients* Vehicle-Controlled (1 year) Vehicle (N=75) N (%)	Adult Active Comparator (1 year) Elidel® Cream (N=328) N (%)
At least 1 AE	182 (68.2%)	97 (71.3%)	241 (72.0%)	230 (84.6%)	56 (74.7%)	256 (78.0%)
Infections and Infestations						
Upper Respiratory Tract Infection NOS	38 (14.2%)	18 (13.2%)	65 (19.4%)	13 (4.8%)	6 (8.0%)	14 (4.3%)
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (9.6%)	72 (26.5%)	16 (21.3%)	25 (7.6%)
Skin Infection NOS	8 (3.0%)	9 (6.6%)	18 (5.4%)	6 (2.2%)	3 (4.0%)	21 (6.4%)
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)	36 (13.2%)	3 (4.0%)	32 (9.8%)
Ear Infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)	9 (3.3%)	1 (1.3%)	2 (0.6%)
Otitis Media	6 (2.2%)	1 (0.7%)	10 (3.0%)	8 (2.9%)	4 (5.3%)	2 (0.6%)
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)	11 (4.0%)	4 (5.3%)	8 (2.4%)
Bacterial Infection	4 (1.5%)	3 (2.2%)	4 (1.2%)	3 (1.1%)	0	6 (1.8%)
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)	6 (2.2%)	3 (4.0%)	20 (6.1%)
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)	6 (2.2%)	1 (1.3%)	2 (0.6%)
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)	0	1 (1.3%)	1 (0.3%)
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)	22 (8.1%)	2 (3.3%)	3 (0.9%)
Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)	0	<1%	0
Molluscum Contagiosum	2 (0.7%)	0	4 (1.2%)	5 (1.8%)	0	0
Staphylococcal Infection	1 (0.4%)	4 (2.9%)	7 (2.1%)	0	<1%	3 (0.9%)
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)	29 (10.7%)	3 (4.0%)	8 (2.4%)
Herpes Simplex	1 (0.4%)	0	4 (1.2%)	9 (3.3%)	2 (2.7%)	13 (4.0%)
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)	17 (6.3%)	0	2 (0.6%)
Viral Infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)	18 (6.6%)	1 (1.3%)	0
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)	20 (7.4%)	2 (2.7%)	6 (1.8%)
Chickenpox	2 (0.7%)	0	3 (0.9%)	8 (2.9%)	3 (4.0%)	1 (0.3%)
Skin Papilloma	1 (0.4%)	0	2 (0.6%)	9 (3.3%)	<1%	0
Tonsillitis Acute NOS	0	0	0	7 (2.6%)	0	0
Upper Respiratory Tract Infection Viral NOS	1 (0.4%)	0	3 (0.9%)	4 (1.5%)	0	1 (0.3%)
Herpes Simplex Dermatitis	0	0	1 (0.3%)	4 (1.5%)	0	2 (0.6%)
Bronchitis Acute NOS	0	0	0	4 (1.5%)	0	0
Eye Infection NOS	0	0	0	3 (1.1%)	<1%	1 (0.3%)
General Disorders and Administration Site Conditions						
Application Site Burning	28 (10.4%)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	1 (0.4%)	3 (4.0%)	21 (6.4%)
Influenza Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)
Application Site Pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)	5 (1.8%)	0	18 (5.5%)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	31 (11.6%)	11 (8.1%)	31 (9.3%)	43 (15.8%)	8 (10.7%)	8 (2.4%)
Nasal Congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)	4 (1.5%)	1 (1.3%)	2 (0.6%)
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)	1 (0.4%)	1 (1.3%)	0
Asthma Aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)	3 (1.1%)	1 (1.3%)	0
Sinus Congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)	<1%	<1%	3 (0.9%)
Rhinitis	1 (0.4%)	0	5 (1.5%)	12 (4.4%)	5 (6.7%)	7 (2.1%)
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)	2 (0.7%)	<1%	0
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)	10 (3.7%)	2 (2.7%)	8 (2.4%)
Epistaxis	0	1 (0.7%)	0	9 (3.3%)	1 (1.3%)	1 (0.3%)
Dyspnea NOS	0	0	0	5 (1.8%)	1 (1.3%)	2 (0.6%)
Gastrointestinal Disorders						
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	10 (3.0%)	15 (5.5%)	5 (6.7%)	1 (0.3%)
Sore Throat	9 (3.4%)	5 (3.7%)	16 (4.8%)	22 (8.1%)	4 (5.3%)	12 (3.7%)
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)	18 (6.6%)	6 (8.0%)	2 (0.6%)
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)	21 (7.7%)	4 (5.3%)	7 (2.1%)
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)	11 (4.0%)	5 (6.7%)	6 (1.8%)
Abdominal Pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)	12 (4.4%)	3 (4.0%)	1 (0.3%)
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)	7 (2.6%)	1 (1.3%)	2 (0.6%)
Constipation	1 (0.4%)	0	2 (0.6%)	10 (3.7%)	<1%	0
Loose Stools	0	1 (0.7%)	4 (1.2%)	<1%	<1%	0
Reproductive System and Breast Disorders						
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)	3 (1.1%)	1 (1.3%)	4 (1.2%)
Eye Disorders						
Conjunctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)	6 (2.2%)	3 (4.0%)	10 (3.0%)
Skin & Subcutaneous Tissue Disorders						
Urticaria	3 (1.1%)	0	1 (0.3%)	1 (0.4%)	<1%	3 (0.9%)
Acne NOS	0	1 (0.7%)	1 (0.3%)	4 (1.5%)	<1%	6 (1.8%)
Immune System Disorders						
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)	14 (5.1%)	1 (1.3%)	11 (3.4%)
Injury and Poisoning						
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)	<1%	1 (1.3%)	0
Laceration	2 (0.7%)	1 (0.7%)	5 (1.5%)	<1%	<1%	0
Musculoskeletal, Connective Tissue and Bone Disorders						
Back Pain	1 (0.4%)	2 (1.5%)	1 (0.3%)	<1%	0	6 (1.8%)
Arthralgias	0	0	1 (0.3%)	3 (1.1%)	1 (1.3%)	8 (2.4%)
Ear and Labyrinth Disorders						
Earache	2 (0.7%)	1 (0.7%)	0	8 (2.9%)	2 (2.7%)	0
Nervous System Disorders						
Headache	37 (13.9%)	12 (8.8%)	38 (11.3%)	69 (25.4%)	12 (16.0%)	23 (7.0%)

*Ages 2-17 years

OVERDOSAGE

There has been no experience of [illegible] (pimecrolimus) Cream 1%. No incidents of [illegible] tion have been reported. If oral ingestion [illegible] advice should be sought.

DOSAGE AND ADMINISTRATION

Apply a thin layer of Elidel® (pimecrolimus) [illegible] the affected skin twice daily and rub in [illegible] pletely. Elidel may be used on all skin [illegible] the head, neck, and intertriginous areas. [illegible] Elidel should be used twice daily for as [illegible] symptoms persist. Treatment should be [illegible] olution of disease occurs. If symptoms [illegible] weeks, the patient should be re-evaluated. The safety of Elidel Cream under occlusion [illegible] mote systemic exposure, has not been [illegible] Cream should not be used with occlusive [illegible]

HOW SUPPLIED

Elidel® (pimecrolimus) Cream 1% is available [illegible] 15 grams, 30 grams, 60 grams, and 100 grams [illegible]

15 gram tube .... [illegible]
30 gram tube .... [illegible]
60 gram tube .... [illegible]
100 gram tube .... [illegible]

Store at 25°C (77°F); excursions permitted [illegible] (59°F-86°F). Do not freeze.

Manufactured by:
Novartis Pharma GmbH
Wehr, Germany

Distributed by:
Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936

REV: APRIL 2003

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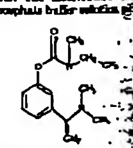
EXELON®
[ex' e-lon]
(rivastigmine tartrate)
Capsules
Rx only

Prescribing Information
The following prescribing information is [illegible] labeling in effect July 2004.

DESCRIPTION

Exelon® (rivastigmine tartrate) is a reversible [illegible] ase inhibitor and is known chemically as [illegible] N-ethyl-3-[1-(dimethylamino)ethyl]-phenyl [illegible] hydrogen-(2R,3R)-tartrate. Rivastigmine [illegible] monly referred to in the pharmacological [illegible] ENA 713 or ENA 713. It has an [illegible] $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ (hydrogen tartrate [illegible] and a molecular weight of 400.43 (hy [illegible] tartrate is a white to off-white, fine [illegible] is very soluble in water, soluble in ethanol [illegible] slightly soluble in n-octanol and very [illegible] ethyl acetate. The distribution co [illegible] n-octanol/phosphate buffer solution pH [illegible]



Exelon is supplied as capsules containing [illegible] trate, equivalent to 1.5, 3, 4.5 and 6 mg [illegible] for oral administration. Inactive [illegible] propyl methylcellulose, magnesium [illegible] the cellulose, and silicon dioxide. Each [illegible] contains gelatin, titanium dioxide [illegible] iron oxides.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pathological changes in Dementia [illegible] volved cholinergic neuronal pathways [illegible] basal forebrain to the cerebral [illegible] These pathways are thought to [illegible] memory, attention, learning and [illegible] While the precise mechanism of [illegible] known, it is postulated to exert [illegible] hancing cholinergic function [illegible] creasing the concentration [illegible]

[illegible] inhibition of its hydrolysis by cholinesterase. If [illegible] mechanism is correct, Exelon's effect may [illegible] disease process advances and fewer cholinergic [illegible] remain functionally intact. There is no evidence [illegible] alters the course of the underlying de[illegible]. After a 6-mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, [illegible] inhibition of about 60% five hours after [illegible]

[illegible] also studies demonstrate that the inhibition [illegible] by rivastigmine is not affected by the co-[illegible] administration of memantine, an N-methyl-D-[illegible] receptor antagonist.

[illegible] of Exelon® (rivastigmine tartrate) as a [illegible] Alzheimer's Disease is demonstrated by the [illegible] randomized, double-blind, placebo-controlled [illegible] igations in patients with Alzheimer's Disease [illegible] (NINCDS-ADRDA and DSM-IV criteria, Mini-[illegible] Examination (MMSE) ≥10 and ≤26, and the [illegible] Deterioration Scale (GDS)). The mean age of pa-[illegible] ipating in Exelon trials was 73 years with a [illegible] Approximately 59% of patients were women [illegible] The racial distribution was Caucasian [illegible] and Other races 3%.

[illegible] Measures: In each study, the effectiveness [illegible] evaluated using a dual outcome assessment [illegible]

[illegible] Exelon to improve cognitive performance was [illegible] the cognitive subscale of the Alzheimer's Dis-[illegible] Scale (ADAS-cog), a multi-item instrument [illegible] extensively validated in longitudinal cohorts [illegible] Disease patients. The ADAS-cog examines [illegible] of cognitive performance including ele-[illegible] memory, orientation, attention, reasoning, lan-[illegible]. The ADAS-cog scoring range is from 0 to [illegible] score indicating greater cognitive impair-[illegible] normal adults may score as low as 0 or 1, but [illegible] for non-demented adults to score slightly [illegible]

[illegible] enrolled as participants in each study had [illegible] ADAS-cog of approximately 23 units, with a [illegible]. Experience gained in longitudinal stud-[illegible] patients with mild to moderate Alzhei-[illegible] suggest that they gain 6-12 units a year on [illegible] lesser degrees of change, however, are seen [illegible] very mild or very advanced disease because [illegible] not uniformly sensitive to change over the [illegible]. The annualized rate of decline in the [illegible] participating in Exelon trials was approx-[illegible] per year.

[illegible] Exelon to produce an overall clinical effect [illegible] a Clinician's Interview Based Impres-[illegible] that required the use of caregiver informa-[illegible] Plus. The CIBIC-Plus is not a single instru-[illegible] standardized instrument like the ADAS-[illegible] for investigational drugs have used a [illegible] formats, each different in terms of depth [illegible] As such, results from a CIBIC-Plus reflect [illegible] from the trial or trials in which it was [illegible] be compared directly with the results of [illegible] Plus evaluations from other clinical trials. The [illegible] in the Exelon trials was a structured in-[illegible] a comprehensive evaluation at baseline [illegible] time-points of three domains: patient cog-[illegible] and functioning, including assessment of [illegible] living. It represents the assessment of a [illegible] using validated scales based on his/her ob-[illegible] interviews conducted separately with the pa-[illegible] familiar with the behavior of the pa-[illegible] interval rated. The CIBIC-Plus is scored as a [illegible] categorical rating, ranging from a score of 1, in-[illegible] improved," to a score of 4, indicating "no [illegible] of 7, indicating "marked worsening." The [illegible] been systematically compared directly [illegible] not using information from caregivers [illegible] global methods.

[illegible] Study

[illegible] duration, 699 patients were random-[illegible] range of 1-4 mg or 6-12 mg of Exelon [illegible] each given in divided doses. The 26-[illegible] divided into a 12-week forced dose titration [illegible] maintenance phase. The patients in [illegible] arms of the study were maintained at [illegible] dose within the respective range.

[illegible] ADAS-cog: Figure 1 illustrates the time [illegible] from baseline in ADAS-cog scores for [illegible] over the 26 weeks of the study. At 26 [illegible] mean differences in the ADAS-cog [illegible] Exelon-treated patients compared to [illegible] were 1.9 and 4.9 units for the [illegible] treatments, respectively. Both treat-[illegible] statistically significantly superior to placebo [illegible] was significantly superior to the [illegible]

[illegible] and optimal

[illegible] cumulative percentages of patients [illegible] treatment groups who had attained [illegible] of improvement in ADAS-cog score [illegible] Three change scores, (7-point) and [illegible] baseline or no change in score) have [illegible] ative purposes, and the percent of [illegible]

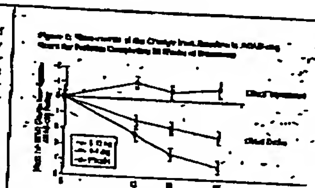


Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

This curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the Exelon groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

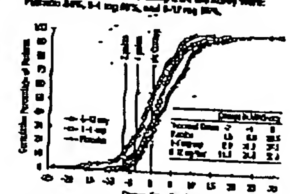


Figure 2: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 1-4 mg 85%, and 6-12 mg 65%.

Effects on the CIBIC-Plus: Figure 3 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients in the mean rating of change from baseline were 0.32 units and 0.35 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day and 1-4 mg/day groups were statistically significantly superior to placebo. The differences between the 6-12 mg/day and the 1-4 mg/day groups were statistically significant.

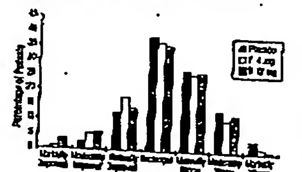


Figure 3: Frequency Distribution of CIBIC-Plus Scores at Week 26

Global Twenty-Six Week Study

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1-4 mg and 6-12 mg treatments, respectively. The 6-12 mg/day group was statistically significantly superior to placebo, as well as to the 1-4 mg/day group. The difference between the 1-4 mg/day group and placebo was not statistically significant.

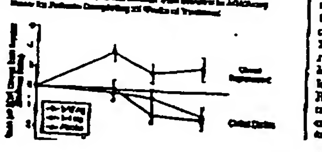


Figure 4: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

Figure 5 illustrates the cu[illegible] from each of the three tre[illegible] at least the measure of i[illegible] shown on the X axis. Simil[illegible] curves demonstrate that b[illegible] and placebo have a wide r[illegible] 6-12 mg/day Exelon group b[illegible] improvements.

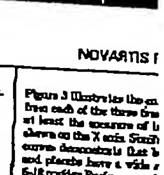


Figure 5: Cumulative Percen[illegible] 26 Weeks of Double-blind Tr[illegible] from Baseline ADAS-cog Sc[illegible] Randomized Patients who C[illegible] Placebo 87%, 1-4 mg 86%, a[illegible]

Effects on the CIBIC-Plus: Fi[illegible] frequency distribution of CIBIC[illegible] tients assigned to each of the [illegible] completed 26 weeks of treatme[illegible] differences for these groups of [illegible] of change from baseline were [illegible] 1-4 mg and 6-12 mg of Exelon, [illegible] ings for the 6-12 mg/day group w[illegible] superior to placebo. The compar[illegible] the 1-4 mg/day group and plac[illegible] cally significant.

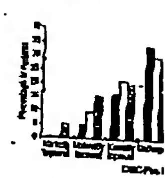


Figure 6: Frequency Distributi[illegible] at Week 26

U.S. Fixed Dose Study

In a study of 26 weeks duration, 7[illegible] ized to doses of 3, 6, or 9 mg/day [illegible] each given in divided doses. The [illegible] which included a 12-week forced t[illegible] week maintenance phase, led to a [illegible] 9 mg/day group because of poor tol[illegible] treatment, significant differences [illegible] ADAS-cog mean change from baseli[illegible] 9 mg/day groups, compared to placel[illegible] ences were observed between any of [illegible] and placebo for the analysis of the C[illegible] of change. Although no significant di[illegible] between Exelon treatment groups, th[illegible] numerical superiority with higher d[illegible]

Age, Gender and Race

Patient's age, gender, or race did n[illegible] come in Exelon treatment.

Pharmacokinetics

Rivastigmine is well absorbed with a[illegible] of about 40% (3-mg dose). It shows li[illegible] up to 3 mg BID but is non-linear at h[illegible] the dose from 3 to 6 mg BID results [illegible] AUC. The elimination half-life is abou[illegible] elimination as metabolites via the uri[illegible]

Absorption: Rivastigmine is rapid[illegible] sorbed. Peak plasma concentrations a[illegible] in about 1 hour. Absolute bioavailabili[illegible] about 36%. Administration of Exelon [illegible] sorption (t_{max}) by 90 min, lowers C_{max} [illegible] and increases AUC by approximately [illegible]

Distribution: Rivastigmine is widely [illegible] out the body with a volume of distribu[illegible] 1.8-2.7 L/kg. Rivastigmine penetrates [illegible] rier, reaching CSF peak concentratio[illegible] Mean AUC_{1-12hr} ratio of CSF/plasma a[illegible] following 1-6 mg BID doses.

Rivastigmine is about 40% bound to pla[illegible] centrations of 1-400 ng/mL, which co[illegible] concentration range. Rivastigmine dist[illegible] tween blood and plasma with a [illegible]

...tion of its hydrolysis by cholinesterase. If ... mechanism is correct, Exelon's effect may ... disease process advances and fewer cholinergic ... functionally intact. There is no evidence ... alters the course of the underlying de... after a 6-mg dose of rivastigmine, anticho... is present in CSF for about 10 hours, ... inhibition of about 60% five hours after ...

... studies demonstrate that the inhibition ... by rivastigmine is not affected by the coad... ministration of memantine, an N-methyl-D-... antagonist.

... of Exelon® (rivastigmine tartrate) as a ... Alzheimer's Disease is demonstrated by the ... randomized, double-blind, placebo-controlled ... in patients with Alzheimer's Disease ... (NINCDS-ADRDA and DSM-IV criteria, Mini-... Examination (MMSE) ≥10 and ≤26, and the ... Scale (GDS)). The mean age of pa... in Exelon trials was 73 years with a ... approximately 59% of patients were women ... The racial distribution was Caucasian ... Other races 9%.

...: In each study, the effectiveness ... evaluated using a dual outcome assessment ...

... to improve cognitive performance was ... cognitive subscale of the Alzheimer's Dis... Scale (ADAS-cog), a multi-item instrument ... extensively validated in longitudinal cohorts ... disease patients. The ADAS-cog examines ... of cognitive performance including ele... orientation, attention, reasoning, lan... The ADAS-cog scoring range is from 0 to ... scores indicating greater cognitive impair... normal adults may score as low as 0 or 1, but ... for non-demented adults to score slightly ...

... recruited as participants in each study had ... ADAS-cog of approximately 23 units, with a ... Experience gained in longitudinal stud... patients with mild to moderate Alzhei... suggest that they gain 6-12 units a year on ... lower degrees of change, however, are seen ... very mild or very advanced disease because ... not uniformly sensitive to change over the ... The annualized rate of decline in the ... participating in Exelon trials was approx... units per year.

... Exelon to produce an overall clinical effect ... using a Clinician's Interview Based Impres... that required the use of caregiver informa... Plus. The CIBIC-Plus is not a single instru... a standardized instrument like the ADAS-... trials in investigational drugs have used a ... formats, each different in terms of depth ... As such, results from a CIBIC-Plus reflect ... from the trial or trials in which it was ... be compared directly with the results of ... evaluations from other clinical trials. The ... in the Exelon trials was a structured in... a comprehensive evaluation at baseline ... points of three domains: patient cog... and functioning, including assessment of ... living. It represents the assessment of a ... validated scales based on his/her ob... were conducted separately with the pa... function with the behavior of the pa... The CIBIC-Plus is scored as a ... rating, ranging from a score of 1, ... improved," to a score of 4, indicating "no ... 7, indicating "marked worsening." The ... been systematically compared directly ... using information from caregivers ... methods.

... Study

... duration, 699 patients were random... range of 1-4 mg or 6-12 mg of Exelon ... each given in divided doses. The 26-... divided into a 12-week forced dose titration ... maintenance phase. The patients in ... arms of the study were maintained at ... dose within the respective range.

...-cog: Figure 1 illustrates the time ... from baseline in ADAS-cog scores for ... over the 26 weeks of the study. At 26 ... the mean differences in the ADAS-cog ... Exelon-treated patients compared to ... were 1.9 and 4.9 units for the ... treatments, respectively. Both treat... significantly superior to placebo ... was significantly superior to the ...

... (... scheme)

... cumulative percentages of patients ... treatment groups who had attained ... of improvement in ADAS-cog score ... Three change scores, (7-point and ... baseline or no change in score) have ... for ...

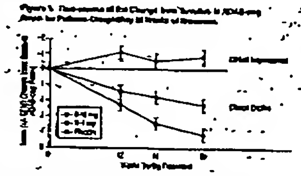
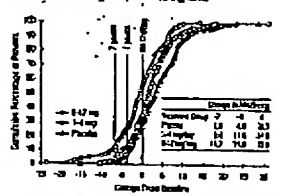


Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

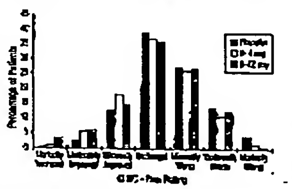
The curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the Exelon groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

Figure 2: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 1-4 mg 85%, and 6-12 mg 65%.



Effects on the CIBIC-Plus: Figure 3 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients in the mean rating of change from baseline were 0.32 units and 0.35 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day and 1-4 mg/day groups were statistically significantly superior to placebo. The differences between the 6-12 mg/day and the 1-4 mg/day groups were statistically significant.

Figure 3: Frequency Distribution of CIBIC-Plus Scores at Week 26



Global Twenty-Six-Week Study

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1-4 mg and 6-12 mg treatments, respectively. The 6-12 mg/day group was statistically significantly superior to placebo, as well as to the 1-4 mg/day group. The difference between the 1-4 mg/day group and placebo was not statistically significant.

Figure 4: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

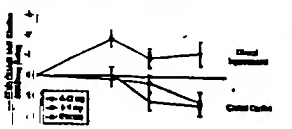
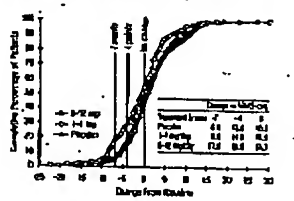


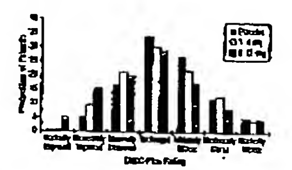
Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Similar to the U.S. 26-week study, the curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the 6-12 mg/day Exelon group is more likely to show the greater improvements.

Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 87%, 1-4 mg 86%, and 6-12 mg 67%.



Effects on the CIBIC-Plus: Figure 6 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients for the mean rating of change from baseline were 0.14 units and 0.41 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day group was statistically significantly superior to placebo. The comparison of the mean ratings for the 1-4 mg/day group and placebo group was not statistically significant.

Figure 6: Frequency Distribution of CIBIC-Plus Scores at Week 26



U.S. Fixed Dose Study

In a study of 26 weeks duration, 702 patients were randomized to doses of 3, 6, or 9 mg/day of Exelon or to placebo, each given in divided doses. The fixed-dose study design, which included a 12-week forced titration phase and a 14-week maintenance phase, led to a high dropout rate in the 9 mg/day group because of poor tolerability. At 26 weeks of treatment, significant differences were observed for the ADAS-cog mean change from baseline for the 9 mg/day and 6 mg/day groups, compared to placebo. No significant differences were observed between any of the Exelon dose groups and placebo for the analysis of the CIBIC-Plus mean rating of change. Although no significant differences were observed between Exelon treatment groups, there was a trend toward numerical superiority with higher doses.

Age, Gender and Race

Patient's age, gender, or race did not predict clinical outcome to Exelon treatment.

Pharmacokinetics

Rivastigmine is well absorbed with absolute bioavailability of about 40% (3-mg dose). It shows linear pharmacokinetics up to 3 mg BID but is non-linear at higher doses. Doubling the dose from 3 to 6 mg BID results in a 3-fold increase in AUC. The elimination half-life is about 1.5 hours, with most elimination as metabolites via the urine.

Absorption: Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. Absolute bioavailability after a 3-mg dose is about 36%. Administration of Exelon with food delays absorption (t_{max}) by 90 min, lowers C_{max} by approximately 30% and increases AUC by approximately 30%.

Distribution: Rivastigmine is widely distributed throughout the body with a volume of distribution in the range of 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Mean AUC_{1-12hr} ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg BID doses.

Rivastigmine is about 40% bound to plasma proteins at concentrations of 1-400 ng/mL, which cover the therapeutic concentration range. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition

[redacted]

Exelon Capsules—Cont.

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Based on evidence from in vitro and animal studies the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions related to cytochrome P450 have been observed in humans (see *Drug-Drug Interactions*).

Elimination: The major pathway of elimination is via the kidneys. Following administration of ^{14}C-rivastigmine to 6 healthy volunteers, total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. No parent drug was detected in urine. The sulfate conjugate of the decarbamylated metabolite is the major component excreted in urine and represents 40% of the dose. Mean oral clearance of rivastigmine is 1.8 ± 0.6 L/min after 6 mg BID.

Special Populations

Hepatic Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6 mg BID oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10). Dosage adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability.

Renal Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR≥60 mL/min); CL/F=1.7 L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients (n=8, GFR<10 mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR≥60 mL/min); CL/F=6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability.

Age: Following a single 2.5 mg oral dose to elderly volunteers (>60 years of age, n=24) and younger volunteers (n=24), mean oral clearance of rivastigmine was 30% lower in elderly (7 L/min) than in younger subjects (10 L/min).

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Exelon, but a population pharmacokinetic analysis indicates that gender (n=277 males and 348 females) and race (n=575 White, 34 Black, 4 Asian, and 12 Other) did not affect the clearance of Exelon.

Nicotine Use: Population PK analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (n=75 Smokers and 549 Nonsmokers).

Drug-Drug Interactions

Effect of Exelon on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on in vitro studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15). In addition, in clinical trials, no increased risk of clinically relevant untoward effects was observed in patients treated concomitantly with Exelon and these agents.

INDICATIONS AND USAGE

Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS

Exelon® (rivastigmine tartrate) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (see DESCRIPTION).

WARNINGS

Gastrointestinal Adverse Reactions

Exelon® (rivastigmine tartrate) use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this rea- [illegible]

BID and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose (see DOSAGE AND ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5-mg dose after 8 weeks of treatment interruption).

Nausea and Vomiting: In the controlled clinical trials, 47% of the patients treated with an Exelon dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Exelon-treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% vs. 3% for placebo) than in the maintenance phase (14% vs. 3% for placebo). The rates were higher in women than men. Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of Exelon-treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs. 9% for placebo) than in the maintenance phase (17% vs. 4% for placebo).

Weight Loss: In the controlled trials, approximately 26% of women on high doses of Exelon (greater than 9 mg/day) had weight loss of equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

Anorexia: In the controlled clinical trials, of the patients treated with an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course nor the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia

Exelon as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions

Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6-12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary

Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions

Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers

Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Drug-Drug Interactions

Effect of Exelon® (rivastigmine tartrate) on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on in vitro studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose phar- [illegible]

rivastigmine is not significantly affected [illegible] ministration of digoxin, warfarin, diaz[illegible] Population PK analysis with a databa[illegible] showed that the pharmacokinetics of [illegible] influenced by commonly prescribed [illegible] antacids (n=77), antihypertensives [illegible] (n=42), calcium channel blockers [illegible] (n=21), nonsteroidal anti-inflammatory [illegible] gens (n=70), salicylate analgesics (n=17[illegible]) (n=35), and antihistamines (n=15) [illegible]

Use with Anticholinergics: Because of [illegible] action, cholinesterase inhibitors have the [illegible] fere with the activity of anticholinergic [illegible]

Use with Cholinomimetics and Other Ch[illegible] tors: A synergistic effect may be expected [illegible] terase inhibitors are given concurrently [illegible] ine, similar neuromuscular blocking [illegible] agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impai[illegible]

In carcinogenicity studies conducted [illegible] 1.1 mg-base/kg/day in rats and 1.6 mg[illegible] rivastigmine was not carcinogenic. The[illegible] proximately 0.9 times and 0.7 times [illegible] mended human daily dose of 12 mg/da[illegible]

Rivastigmine was clastogenic in two [illegible] presence, but not the absence, of meta[illegible] caused structural chromosomal aberr[illegible] Hamster lung cells and both structural [illegible] ploidy) chromosomal aberrations in human [illegible] lymphocytes. Rivastigmine was not gen[illegible] tro assays: the Ames test, the unsche[illegible] (UDS) test in rat hepatocytes (a test [illegible] repair synthesis), and the HGPRT test [illegible] ster cells. Rivastigmine was not clast[illegible] mouse micronucleus test.

Rivastigmine had no effect on fertility [illegible] formance in the rat at dose levels up to [illegible] This dose is approximately 0.9 times th[illegible] mended human daily dose of 12 mg/day [illegible]

Pregnancy

Pregnancy Category B: Reproduction [illegible] pregnant rats at doses up to 2.3 mg-b[illegible] mately 2 times the maximum recomm[illegible] 4 mg/m² basis) and in pregnant rab[illegible] 2.3 mg-base/kg/day (approximately 4 t[illegible] recommended human dose on a mg/m² [illegible] evidence of teratogenicity. Studies in [illegible] decreased fetal/pup weights, usually [illegible] maternal toxicity; decreased weights [illegible] which were several fold lower than the [illegible] mended human dose on a mg/m² basis [illegible] quate or well-controlled studies in pre[illegible] cause animal reproduction studies are not [illegible] of human response, Exelon should be [illegible] nancy only if the potential benefit jus[illegible] to the fetus.

Nursing Mothers

It is not known whether rivastigmine is [illegible] breast milk. Exelon has no indication [illegible] mothers.

Pediatric Use

There are no adequate and well-controll[illegible] ing the safety and efficacy of Exelon in [illegible] in children.

ADVERSE REACTIONS

Adverse Events Leading to Discontinu[illegible]

The rate of discontinuation due to adv[illegible] trolled clinical trials of Exelon® (rivastigmine [illegible]) 15% for patients receiving 6-12 mg/da[illegible] patients on placebo during forced [illegible] While on a maintenance dose, the [illegible] patients on Exelon compared to 4% [illegible] The most common adverse events le[illegible] tion, defined as those occurring in at [illegible] and at twice the incidence seen in [illegible] shown in Table 1.

[See table 1 at top of next page]

Most Frequent Adverse Clinical E[illegible] with the Use of Exelon

The most common adverse events, [illegible] ring at a frequency of at least 5% [illegible] are largely predicted by Exelon's [illegible] include nausea, vomiting, [illegible] asthenia.

Gastrointestinal Adverse Reac[illegible] ated with significant nausea, vo[illegible] WARNINGS).

Adverse Events Reported in Con[illegible]

Table 2 lists treatment emergent [illegible] were reported in at least 2% [illegible] controlled trials and for which [illegible] greater for patients treated with [illegible] day than for those treated with [illegible] should be aware that these figure[illegible] the frequency of adverse events in [illegible] ical practice when patient charac[illegible] may differ from those prevailin[illegible] Similarly, the cited frequencies [illegible] with figures obtained from other [illegible] volving different treatments, [illegible]

Table 1

[illegible] Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced Dose Titration

[illegible]	Titration Placebo (n=868)	Titration Exelon ≥6-12 mg/day (n=1,189)	Maintenance Placebo (n=788)	Maintenance Exelon ≥6-12 mg/day (n=987)	Overall Placebo (n=868)	Overall Exelon ≥6-12 mg/day (n=1,189)
[illegible]	<1	8	<1	1	1	8
[illegible]	<1	4	<1	1	<1	5
[illegible]	0	2	<1	1	<1	3
[illegible]	<1	2	<1	1	<1	2

[illegible] basis by which to estimate the relative [illegible] drug and non-drug factors to the adverse [illegible] in the population studied.

[illegible] reactions were less frequent later in the [illegible]

[illegible] of race or age could be determined on [illegible] adverse events in the controlled studies. [illegible] and weight loss were more frequent in [illegible]

Table 2

[illegible] Reported in Controlled Clinical [illegible] at Least 2% of Patients Receiving [illegible] (6-12 mg/day) and at a Higher [illegible] than Placebo-treated Patients

[illegible] Event	Placebo (n=868)	Exelon (6-12 mg/day) (n=1,189)
[illegible] with any [illegible]	79	92
[illegible] System		
[illegible]	1	4
[illegible]	2	3
[illegible]		
[illegible]	9	10
[illegible]	5	9
[illegible]	2	6
[illegible]	2	5
[illegible]	2	3
[illegible]	<1	3
[illegible], Overall		
[illegible]	2	3
[illegible] Nervous System		
[illegible]	11	21
[illegible]	12	17
[illegible]	3	5
[illegible]	1	4
[illegible]		
[illegible]	12	47
[illegible]	6	31
[illegible]	11	19
[illegible]	3	17
[illegible]	6	13
[illegible]	4	9
[illegible]	4	5
[illegible]	2	4
[illegible]	1	2
[illegible]		
[illegible]	7	9
[illegible]	7	8
[illegible]	4	6
[illegible]	3	5
[illegible]	1	4
[illegible]	1	3
[illegible] Disorders		
[illegible]	6	7
[illegible]		
[illegible]	3	4

[illegible] occurred at a rate of 2% or more on [illegible] at a greater or equal rate on placebo [illegible] edema, vertigo, back pain, ar[illegible], agitation, nervousness, deli[illegible], upper respiratory tract infection, [illegible], pharyngitis, bronchitis, rash [illegible]

[illegible] Observed During Clinical Trials

[illegible] to over 5,297 individuals dur[illegible]. Of these, 4,326 patients have [illegible] months, 3,407 patients have been [illegible] months, 2,150 patients have been [illegible] have been treated for 2 years, and [illegible] over 3 years. With regard to ex[illegible] 1,908 patients were exposed to [illegible] patients treated for 3 months, [illegible] months, 1,370 patients treated [illegible] for 1 year, and 129 treated [illegible]

[illegible] and symptoms that occurred [illegible] trials and 9 open-label trials in [illegible] Europe, Australia, South Africa, [illegible] adverse events by the [illegible]

investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5,297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paraesthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goiter, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, dermatitis contact.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders [illegible]

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As Exelon® (rivastigmine tartrate) has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8-10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Exelon should be administered for the next 24 hours.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when coadministered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of Exelon, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46 mg overdose with Exelon, the patient experienced vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

DOSAGE AND ADMINISTRATION

The dosage of Exelon® (rivastigmine tartrate) shown to be effective in controlled clinical trials is 6-12 mg/day, given as twice a day dosing (daily doses of 3 to 6 mg BID). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

The starting dose of Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (see WARNINGS). The maximum dose is 6 mg BID (12 mg/day).

Exelon should be taken with meals in divided doses in the morning and evening.

HOW SUPPLIED

Exelon® (rivastigmine tartrate) capsules equivalent to 1.5 mg, 3 mg, 4.5 mg, or 6 mg of rivastigmine base are available as follows:

1.5 mg Capsule – yellow, "Exelon 1,5 mg" is printed in red on the body of the capsule.

Bottles of 60 .... NDC 0078-0323-44
Bottles of 500 .... NDC 0078-0323-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0323-06

3 mg Capsule – orange, "Exelon 3 mg" is printed in red on the body of the capsule.

Bottles of 60 .... NDC 0078-0324-44
Bottles of 500 .... NDC 0078-0324-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0324-06

4.5 mg Capsule – red, "Exelon 4,5 mg" is printed in white on the body of the capsule.

Bottles of 60 .... NDC 0078-0325-44
Bottles of 500 .... NDC 0078-0325-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0325-06

6 mg Capsule – orange and red, "Exelon 6 mg" is printed in red on the body of the capsule.

Bottles of 60 .... NDC 0078-0326-44
Bottles of 500 .... NDC 0078-0326-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0326-06

Store below 77°F (25°C) in a tight container.

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Shown in Product Identification Guide, page [illegible]

...FORMATION

Table 1
...st Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced Dose Titration

	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1,189)	Placebo (n=788)	Exelon ≥6-12 mg/day (n=987)	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1,189)
...ding	<1	8	<1	1	1	8
[illegible]	<1	4	<1	1	<1	5
[illegible]	0	2	<1	1	<1	3
[illegible]	<1	2	<1	1	<1	2

...basis by which to estimate the relative ...drug and non-drug factors to the adverse ...in the population studied.
...ces were less frequent in the ...
...of race or age could be determined on ...adverse events in the controlled studies. ...and weight loss were more frequent in ...

Table 2
...ents Reported in Controlled Clinical ...at Least 2% of Patients Receiving ...(6-12 mg/day) and at a Higher ...than Placebo-treated Patients

...Adverse Event	Placebo (n=868)	Exelon (6-12 mg/day) (n=1,189)
...ts with any ...	79	92
...System		
...ed	1	4
	2	3
...		
...	9	10
	5	9
	2	6
	2	5
...Symptoms	2	3
	<1	3
...Disorders, General		
	2	3
...al Nervous System		
	11	21
	12	17
	3	5
	1	4
...System		
	12	47
	6	31
	11	19
	3	17
	6	13
	4	9
	4	5
	2	4
	1	2
...		
	7	9
	7	8
	4	6
	3	4
	3	4
	2	3
...Disorders		
...Infection	6	7
...		
	3	4

...observed at a rate of 2% or more on ...but at a greater or equal rate on placebo ...ripheral edema, vertigo, back pain, ar...fracture, agitation, nervousness, delu...upper respiratory tract infections, ...pharyngitis, bronchitis, rash...

...Observed During Clinical Trials
...to some 5,297 individuals (for...). Of these, 4,326 patients have ...months, 3,407 patients have been ...months, 2,150 patients have been ...have been treated for 2 years, and ...for over 3 years. With regard to ex...1,300 patients were exposed to ...patients treated for 6 months, ...dose months, 1,876 patients treated ...treated for 2 years, and 129 treated ...

...and symptoms that occurred ...trials and 9 open-label trials in ...Europe, Australia, South Africa, ...adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5,297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paresthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goiter, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, dermatitis contact.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As Exelon® (rivastigmine tartrate) has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8-10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Exelon should be administered for the next 24 hours.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when coadministered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of Exelon, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46 mg overdose with Exelon, the patient experienced vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

DOSAGE AND ADMINISTRATION

The dosage of Exelon® (rivastigmine tartrate) shown to be effective in controlled clinical trials is 6-12 mg/day, given as twice a day dosing (daily doses of 3 to 6 mg BID). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

The starting dose of Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (see WARNINGS). The maximum dose is 6 mg BID (12 mg/day).

Exelon should be taken with meals in divided doses in the morning and evening.

HOW SUPPLIED

Exelon® (rivastigmine tartrate) capsules equivalent to 1.5 mg, 3 mg, 4.5 mg, or 6 mg of rivastigmine base are available as follows:

1.5 mg Capsule – yellow, "Exelon 1,5 mg" is printed in red on the body of the capsule.

Bottles of 60 .... NDC 0078-0323-44
Bottles of 500 .... NDC 0078-0323-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0323-06

3 mg Capsule – orange, "Exelon 3 mg" is printed in red on the body of the capsule.

Bottles of 60 .... NDC 0078-0324-44
Bottles of 500 .... NDC 0078-0324-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0324-06

4.5 mg Capsule – red, "Exelon 4,5 mg" is printed in white on the body of the capsule.

Bottles of 60 .... NDC 0078-0325-44
Bottles of 500 .... NDC 0078-0325-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0325-06

6 mg Capsule – orange and red, "Exelon 6 mg" is printed in red on the body of the capsule.

Bottles of 60 .... NDC 0078-0326-44
Bottles of 500 .... NDC 0078-0326-08
Unit Dose (blister pack)
Box of 100 (strips of 10) .... NDC 0078-0326-06

Store below 77°F (25°C) in a tight container.

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Shown in Product Identification Guide, page 325

Continued on next page

FDA rejects memantine for mild Alzheimer's

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July 26, 2005

The U.S. Food and Drug Administration (FDA) declined to approve memantine (Namenda) to treat mild Alzheimer's disease, Forest Laboratories announced today.

Memantine was approved to treat moderate to severe Alzheimer stages in 2003.

Forest has conducted three studies of memantine as a treatment for mild to moderate Alzheimer's. In one study, participants taking memantine fared better than those receiving a placebo on tests of memory and thinking skills as well as on assessments by their physicians and caregivers. In two other studies, memantine failed to show any statistically significant benefit compared with the placebo. In one of the studies that failed to show benefit, participants were already on a stable dose of a cholinesterase inhibitor at the time they began taking memantine.

For more information, please see:

- Alzheimer's Association **fact sheet** on memantine
- Forest Laboratories **press release** about FDA's rejection of memantine for mild Alzheimer's disease
- A Medscape **news article** on the study in mild Alzheimer's disease that found a statistically significant benefit for memantine
  (free registration required to access article)

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225 N. Michigan Ave., Fl. 17, Chicago, IL 60601
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alzheimer's

Seal of Ap

CME

Efficacy of donepezil in mild cognitive impairment

A randomized placebo-controlled trial

S. Salloway, MD, MS; S. Ferris, PhD; A. Kluger, PhD; R. Goldman, PhD; T. Griesing, PhD; D. Kumar, MS; and S. Richardson, PhD, for the Donepezil "401" Study Group*

Abstract—*Objective:* To evaluate the efficacy and safety of the acetylcholinesterase inhibitor donepezil in a placebo-controlled trial in patients with mild cognitive impairment (MCI). *Methods:* A total of 270 patients with MCI were enrolled in a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Patients were randomized to receive donepezil (n = 133; 5 mg/day for 42 days, followed by forced dose escalation to 10 mg/day) or placebo (n = 137). Primary efficacy measures were the New York University (NYU) Paragraph Delayed Recall test and the Alzheimer disease (AD) Cooperative Study Clinician's Global Impression of Change for MCI (ADCS CGIC-MCI). Secondary efficacy measures included the modified AD Assessment Scale-cognitive subscale (ADAS-cog), the Patient Global Assessment (PGA), and additional neuropsychologic measures. Efficacy analyses were performed on intent-to-treat (ITT) and fully evaluable (FE) populations. *Results:* Primary efficacy measures of the NYU Paragraph Recall test and the ADCS CGIC-MCI did not show significant treatment effects in the ITT population. Some secondary measures showed effects favoring donepezil. More donepezil-treated patients showed improvements in ADAS-cog total scores, in tests of attention and psychomotor speed, and in PGA scores. More donepezil-treated than placebo-treated patients experienced adverse events, most of which were mild to moderate and transient. *Conclusion:* Although significant treatment effects were not seen in the primary efficacy measures, outcomes on secondary measures suggest promising directions for further evaluation of donepezil treatment in patients with MCI.

NEUROLOGY 2004;63:651–657

Mild cognitive impairment (MCI) is currently an area of considerable clinical and research interest because of the high rate of conversion from MCI to Alzheimer disease (AD).[1-4] Several studies have demonstrated that patients with MCI progress to AD at a higher rate (10 to 15% per year) than normal elderly patients (1 to 3% per year). Therefore, MCI patients are considered to be at a higher risk for AD. MCI may be classified as amnestic, single non-memory domain impaired, or multiple domains slightly impaired.[5] Amnestic MCI is distinguished by impairment of episodic memory. Compared with normal aging, amnestic MCI is associated with a high degree of memory impairment with little or no impairment in activities of daily living (ADLs).[5,10] Individuals with amnestic MCI do not meet the currently accepted clinical criteria for probable AD.

The high rate of conversion from MCI to AD makes early diagnosis and treatment important clinical issues. In its earliest stages, AD manifests primarily as cognitive impairment. As AD progresses, there is further loss of cognitive abilities, a loss of functional independence, and the development of behavioral problems.[11] Early diagnosis and treatment may delay the onset of these symptoms.

Extensive data support the use of cholinesterase inhibitors (ChEIs), including tacrine, donepezil, rivastigmine, and galantamine, for the treatment of mild to moderate AD.[12-16] While the patients in these studies were treated for up to 6 months, other studies of donepezil treatment of 1 year duration further support the long-term benefits on cognition and function in patients with mild to moderate AD.[17,18] Reduction in risk for nursing home placement is

* Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the August 24 issue to find the title link for this article.

* Members of the Donepezil "401" Study Group are listed in the Appendix on page 656.

From the Department of Clinical Neurosciences (Dr. Salloway), Brown University, Providence, RI; Silberstein Institute for Aging and Dementia (Drs. Ferris and Kluger), New York University School of Medicine, New York; Department of Psychology (Dr. Kluger), Lehman College, CUNY, Bronx, NY; Pfizer Inc. (Drs. Goldman and Griesing), New York, NY, and Eisai Inc. (D. Kumar and Dr. Richardson), Teaneck, NJ.

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associated with longer-term donepezil use (at least 9 to 12 months of treatment).[19,20] In a study of patients with early-stage AD, donepezil-treated patients (mean Mini-Mental State Examination [MMSE], 24.1 ± 1.7) showed improvement in cognitive status compared with placebo-treated patients (mean MMSE, 24.3 ± 1.3).[21] Additional data from clinical studies with physostigmine[22] and donepezil[23] have shown enhancement of memory in nondemented individuals, suggesting that benefits may be possible even in individuals with the mildest symptoms of AD or MCI.

Based on the demonstrated treatment benefits of donepezil in mild to moderately severe AD, the present study was conducted to further evaluate the efficacy and safety of donepezil on cognitive impairment in patients with an amnestic form of MCI. One of the goals of this study was to determine appropriate study end points to evaluate efficacy in this patient population. Because there is no established methodology to study MCI, the approach established in AD research was adopted. Both global and cognitive measures were selected based on their potential sensitivity to drug treatment effects in patients with MCI. In addition, a battery of neuropsychologic measures was used to evaluate subjects with MCI on tests of attention and psychomotor speed.

Methods. *Patient population.* Men and women with MCI between 55 and 90 years of age, generally healthy and living independently, and capable of complying with testing procedures were enrolled. All patients had a documented memory complaint representing a change from previous functioning, with MMSE[24] scores ≥24. In addition, the global Clinical Dementia Rating (CDR)[25] score was required to be 0.5 with memory box scores of 0.5 or 1, no more than two box scores other than memory rated as high as 1, and no box score rated greater than 1. ADLs were required to be normal or only slightly impaired, as defined by a summed score ≤1.5 on the three functional CDR domains (home and hobbies, community affairs, and personal care). Patients could not have depressive symptoms and had a 17-item Hamilton Rating Scale for Depression (HAM-D) score ≤12.[26] Scores on Paragraph A of the Logical Memory II Delayed Paragraph Recall subtest of the Wechsler Memory Scale–Revised (WMS-R)[27] were required to be below predetermined educational level cut-off scores: ≤8 for ≥16 years of education, ≤4 for 8 to 15 years of education, and ≤2 for 0 to 7 years of education. A modified Hachinski Ischemia Scale[28] score was required to be ≤4.

Participants with a diagnosis of probable or possible AD were excluded. Drug or alcohol abuse or dependence within the previous 5 years was not permitted, as defined by criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text revision* (DSM-IV-TR).[29] Enrollment was not permitted for patients with poorly controlled diabetes or other medical conditions judged to be incompatible with study participation. Previous treatment with donepezil or other ChEIs (e.g., rivastigmine, tacrine, metrifonate, galantamine, physostigmine) was not permitted.

The study was conducted over a 22-month period from March 1999 to December 2000 and was carried out in compliance with the Declaration of Helsinki and its amendments. Written informed consent was obtained from patients and their legal representatives and informants.

Study design. This 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 22 study centers in the United States. Patients were randomized in a 1:1 ratio to receive either donepezil or placebo, administered orally each evening just prior to bedtime. Patients received donepezil 5 mg daily for 42 days, followed by 10 mg daily for the remainder of the study. Following the forced dose escalation, patients unable to tolerate 10 mg donepezil were discontinued from the study. Efficacy and safety were assessed at screening, baseline, and at 6-week intervals thereafter through week 24 (final study visit), or at an early termination visit. During the study, flexibility of dosing in the morning or at bedtime was allowed.

Outcome measures. Primary efficacy measures. The primary efficacy measure for cognitive function was the change from baseline to end point on the New York University (NYU) Paragraph Test Delayed Recall.[9] Different versions of the NYU Paragraph Test Delayed Recall test were used in each test period when retesting the subjects. The different versions were used in a standard order in both placebo and donepezil groups to eliminate memory and order effects.

The primary efficacy measure for global function was the change from baseline to end point on the AD Cooperative Study's Clinical Global Impression of Change (ADCS-CGIC) instrument.[30] The CGIC-MCI, adapted from the ADCS CGIC, is a clinical global impression of change scale for use with patients with MCI based on semistructured interviews from both the subject and an informant. The CGIC rating is made on a 7-point Likert-type scale, where the clinician's impression of change from baseline is rated as marked improvement (1) to no change (4) to marked worsening (7).

Secondary efficacy measures. Secondary measures of cognitive function included a modified 13 item AD Assessment Scale cognitive subscale (ADAS-cog),[31] the WMS-R Digit Span Backwards test,[27] the Symbol Digit Modalities test,[32] and the NYU Paragraph Test Immediate Recall.[9] Other secondary measures of the neuropsychologic test battery included the modified Boston Naming Task,[33] the Verbal Fluency test,[34] the Maze test,[35] and the Number Cancellation test.[36] Modifications to the original ADAS-cog test included the use of 12 words in the Word Recall test rather than 10, the addition of Delayed Word Recall, the reduction in number of trials of the Word Recognition Task from 3 to 1, and the addition of a Concentration/Distractibility item.[30]

In the secondary measure of global function, patients were asked to rate their own perception of change in memory since onset of treatment using the Patient Global Assessment (PGA). The PGA is a 7-point Likert-type scale in which scores range from very much improved (1) to no change (4) to very much worse (7).

Safety measures. The safety and tolerability of treatments were assessed by monitoring adverse events, vital signs, physical examination findings, EKG abnormalities, and evaluation of clinical laboratory measures.

Data analysis. A sample size of 110 patients per treatment group was estimated based on detection of differences between placebo and drug treatment on primary efficacy variables (0.4 on the CGIC-MCI and 1.0 on the NYU Paragraph Delayed Recall) with 80% power at a 0.05 significance level. Sample size was increased by 20% to 130 per group as a result of a greater than expected premature discontinuation rate.

Analyses of efficacy were performed on the intent-to-treat (ITT) population using the last observation carried forward (LOCF) method for missing data points. The ITT population included all patients randomized to treatment who received at least one dose of study medication, had a baseline evaluation, and at least one evaluation for the primary efficacy measure. The ITT-LOCF population included all subjects who received at least one dose of medication and had at least one pretreatment evaluation and one evaluation after the start of treatment. Efficacy of donepezil treatment in the ITT LOCF population was considered to be the primary outcome measure.

Efficacy of donepezil treatment was also analyzed in the ITT-Observed Cases (OC) and the fully evaluable (FE) population. The ITT-OC population included all subjects who received at least one dose of medication, had a baseline evaluation, and had a double-blind treatment evaluation at week 24 irrespective of compliance and protocol violations. The FE population consisted of all patients who completed 24 weeks of treatment, with ≥80% compliance at the week 24 visit and at two other clinic visits, and no significant protocol violations. Because this study also aimed to establish methodology to study MCI, analyses of treatment effect in the OC and FE population were conducted to further evaluate the sensitivity of the selected cognitive and functional measures to donepezil treatment in patients with MCI. In addition, evaluation of the FE population was used to assess treatment effect in the patient population that best complied with the treatment protocol.

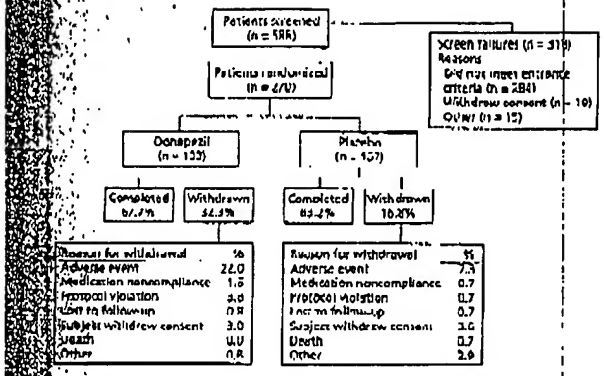

Figure 1 *Patient enrollment and completion through the study.*

Analyses of safety were performed using the safety population, which included all subjects who were randomized and took at least one dose of study medication.

Continuous variables were assessed using analysis of variance (ANCOVA) models. Statistical analyses of efficacy measures were performed on the change from baseline scores at weeks 6, 12, 18, and 24 (OC) and at end point (LOCF). The overall treatment effect was assessed by the analysis using type III sums of squares performed at the 5% level to determine significance. Ordinal variables were analyzed using the Cochran-Mantel-Haenszel χ^2 test with MODRIDITS scores. Treatment differences in the incidence rates for adverse events were tested using Fisher's exact test. Statistical tests were two-tailed, and a value of 0.05 or below was accepted as an indicator of significance.

Results. *Demographic characteristics.* A total of 270 MCI subjects were randomized, of which 133 received donepezil and 137 received placebo (figure 1). Subjects in both the donepezil and placebo groups received study medication for a median of 168 days. Ninety patients from the donepezil group (67.7%) and 114 patients from the placebo group (83.2%) completed the study. Discontinuations were similar in the two study groups between baseline and week 6, but discontinuations increased in the donepezil group following dose escalation after week 6.

Subject characteristics at baseline are summarized in table 1. Subjects randomized to the donepezil and placebo groups were similar with respect to age, sex, race, education, and baseline neuropsychologic and cognitive test scores (e.g., CDR, MMSE, WMS-R, modified ADAS-cog, and NYU Paragraph Delayed Recall). The scores on the HAM-D were low (≤2) in both treatment groups. Donepezil-treated patients had slightly more abnormal physical examination findings at screening, but were similar with respect to other common medical comorbidities. Use of concomitant medications was reported in nearly all patients (98.5% of donepezil group and 96.4% of placebo group).

Primary efficacy measures. On the NYU Delayed Paragraph Recall test, no significant treatment effects were observed in the ITT-LOCF (table 2) and ITT-OC analyses. In measures of global function, the least squares mean CGIC-MCI scores were better for donepezil-treated than placebo-treated subjects at end point, but the differences were not significant in the ITT or FE populations. In the ITT OC population, 32.6% of donepezil-treated subjects showed minimal or moderate improvement, compared with 24.8% of placebo-treated subjects; 51.7% of donepezil-treated and 60.4% of placebo-treated subjects showed no change. These proportions were similar in the FE population.

Table 1 *Summary of baseline demographic characteristics and neuropsychologic test scores for the safety population*

Characteristic	Donepezil, n = 133	Placebo, n = 137
Mean age, y ± SD (range)	72.1 ± 8.0 (55–89)	73.7 ± 8.0 (55–89)
Female patients, n (%)	56 (42.1)	58 (42.3)
Race, white, n (%)	127 (95.2)	127 (93.7)
Education, y, mean ± SD	14.9 ± 2.8	15.0 ± 2.8
Test scores, mean ± SD		
MMSE	27.5 ± 2.2	27.4 ± 2.0
HAM-D	2.0 ± 2.4	2.0 ± 2.4
NYU Paragraph Delayed Recall	3.9 ± 3.0	4.1 ± 3.0
ADAS-cog/13 total (85 max)	20.0 ± 6.2	19.5 ± 6.9
WMS-R Digit Span Backwards	6.7 ± 2.2	7.0 ± 2.1
Symbol Digit Modalities (no. correct)	33.8 ± 11.0	35.1 ± 11.6

MMSE = Mini-Mental State Examination; HAM-D = Hamilton Rating Scale for Depression; NYU = New York University; ADAS-cog = Alzheimer Disease Assessment Scale–cognitive subscale; WMS-R = Wechsler Memory Scale-Revised.

Secondary efficacy measures. Donepezil treatment was associated with greater improvement on the mean change from baseline on the modified ADAS-cog total score compared with placebo in all populations (ITT-LOCF, ITT-OC, and FE) (figure 2A, see table 2). In the end point analysis, improvements on the ADAS-cog of 7 points or greater were seen in 22.3% of donepezil-treated subjects and in 12.1% of placebo-treated subjects. Improvements of 4 points or greater compared with baseline were seen in 50.0% of donepezil-treated subjects and in 31.8% of placebo-treated subjects (figure 2B). A significant improvement was seen in the donepezil-treated group in the NYU Paragraph Delayed Recall test at week 24 in the FE population. Greater improvements were also observed on the WMS-R Digit Span Backwards test and Symbol Digit Modalities test for subjects receiving donepezil compared with placebo in the FE group (see table 2 and figures E-1A and E-1D, available on the *Neurology* Web site; go to www.neurology.org). No significant differences were observed on the Boston Naming task, Verbal Fluency test, Maze test, and Number Cancellation test in any of the study populations. There was no difference in the patients' self-rating of their memory on the PGA in the ITT-LOCF population. The mean PGA scores at week 24 significantly favored donepezil in the OC and FE groups.

Safety. The discontinuation rate due to adverse events was 8.0% in the placebo group and 22.0% in the donepezil

Table 2 Changes in primary and secondary outcomes after 24 weeks

	Donepezil			Placebo		
Psychometric test: change from baseline ± SE	ITT-LOCF, n = 180	ITT-OC, n = 89	FE, n = 83	ITT-LOCF, n = 152	ITT-OC, n = 110	FE, n = 100
Primary efficacy measure						
NYU Paragraph Test Delayed Recall	0.8 ± 0.3	1.1 ± 0.4	0.9 ± 0.4*	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.3
Secondary efficacy measures						
ADAS-cog/18 item (total)	−3.1 ± 0.5†	−3.3 ± 0.5*	−3.2 ± 0.5†	−1.2 ± 0.5	1.0 ± 0.4	−1.0 ± 0.5
NYU Paragraph Test Immediate Recall	0.8 ± 0.3	1.2 ± 0.3*	1.1 ± 0.3*	0.3 ± 0.3	0.2 ± 0.2	0.3 ± 0.3
WMS-R Digit Span Backwards	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2*	0.1 ± 0.2	0.0 ± 0.2	−0.1 ± 0.2
Symbol Digit Modalities (no. correct)	4.4 ± 0.7	4.5 ± 0.9	4.9 ± 0.9*	3.7 ± 0.6	2.4 ± 0.6	2.2 ± 0.7

*$p \leq 0.05$ and †$p \leq 0.01$ vs placebo.

ITT = intent-to-treat population; LOCF = last observation carried forward; OC = observed cases analysis; FE = fully evaluable population; NYU = New York University; ADAS-cog = Alzheimer Disease Assessment Scale 18-item cognitive subscale; WMS-R = Wechsler Memory Scale–Revised.

group, with most discontinuations occurring after the forced dose escalation from 5 mg to 10 mg. Overall, adverse events occurred in 87.0% of patients in the donepezil group and 79.0% of patients in the placebo group. The most common adverse events, reported by 5% of donepezil-treated subjects and at a minimum of twice the rate of placebo, are listed in table 3. Study medication-related adverse events significantly more common in donepezil-treated subjects than placebo-treated subjects included diarrhea, abnormal dreams, nausea, leg cramps, and vomiting. Most adverse events were transient and only mild or moderate in severity. Five patients in the donepezil group and six patients in the placebo group experienced serious adverse events; only one serious adverse event (atrial fibrillation) was considered possibly related to study medication. No notable changes were reported from baseline to end point in laboratory examination, EKG, physical examination, or vital signs findings.

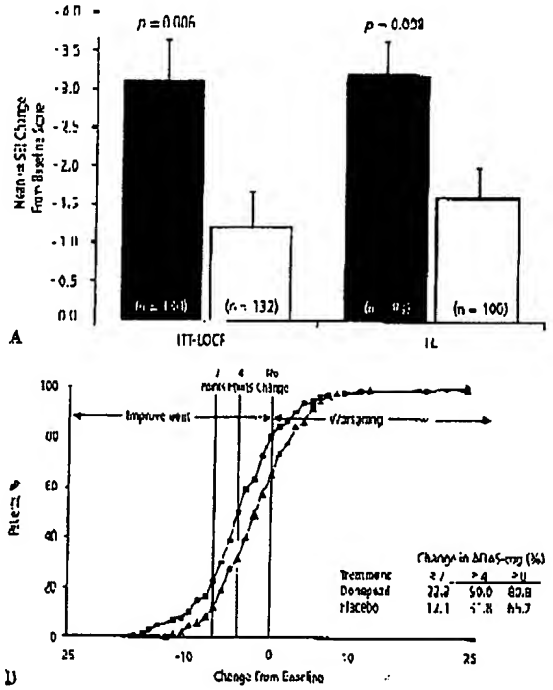

Figure 2. (A) Mean (±SE) change from baseline in modified AD Assessment Scale–cognitive subscale (ADAS-cog) total test scores for the donepezil- and placebo-treated patients in the intent-to-treat last observation carried forward (ITT-LOCF) and fully evaluable (FE) populations. Filled bars = donepezil; open bars = placebo. (B) Cumulative percentage of patients with specified changes from baseline in the mean change from baseline in ADAS cog score in donepezil- and placebo-treated patients. ■ = donepezil; ▲ = placebo.

Discussion. The identified patient population for this study was characterized as having an amnestic form of MCI.[1,6] The patients had memory deficits, which distinguish them from normal aging adults, and did not display significant depressive symptoms, as indicated by low HAM D scores. Functional impairments characteristic of early AD[1,8] were nearly absent, as indicated by the low scores on the CDR ADL domains.

On the primary outcome measures of cognition and clinician-rated global change, significant improvements were not observed in the donepezil group compared with the placebo group in the ITT populations. On the primary cognitive outcome, the NYU Paragraph Delayed Recall test, there was no significant drug-placebo difference in the ITT population. The NYU Paragraph Delayed Recall test is useful in screening patients who are at increased risk for developing dementia or AD.[9] This is a difficult test,

Table 3 Adverse events occurring in ≥5% of patients receiving donepezil and at a minimum of twice the rate of placebo, n (%)

Adverse events	Donepezil, n = 132	Placebo, n = 137
Any	116 (87.9)*	100 (73.0)
Diarrhea	36 (27)*	10 (7)
Nausea	20 (15)*	9 (7)
Vomiting	12 (9)*	0 (0)
Leg cramps	12 (9)*	2 (1)
Abnormal dreams	30 (23)*	5 (4)
Depression	6 (5)	1 (1)
Insomnia	14 (11)	7 (5)

* $p \leq 0.03$ vs placebo.

even for normal individuals, with points given only for verbatim recall of phrases. Because therapeutic interventions for MCI should be directed at those individuals who are at the highest risk for developing AD, this discriminating measure appears useful. However, possible floor effects due to the relative difficulty of the test appear to limit usefulness for detecting treatment effects within the MCI population.

The CGIC-MCI was chosen as the primary efficacy measure of global function based on its validity and reliability in this population.[20,21] The ADCS CGIC-MCI scores were better for donepezil-treated than placebo-treated patients but the differences were not significant. Because the defining feature of amnestic MCI is an isolated memory complaint, the absence of a significant effect on the CGIC-MCI is most likely due to minimal global impairment at baseline and limited decline in global function during a 6-month interval. However, this tool may have utility in longer-term studies because additional clinical symptoms (i.e., function, behavior, mood disturbances) may emerge in MCI subjects over longer observation periods. Although clinicians were not able to detect a significantly greater global response to donepezil treatment, the subjects themselves were able to detect treatment effects. In analyses of subjects completing 24 weeks of treatment (both the OC and FE populations), those treated with donepezil subjectively reported greater improvement in memory function than those given placebo. The majority of donepezil treated subjects reported feeling sharper mentally, more organized, and more confident of their memory.

Evidence of the cognitive benefits of donepezil was observed in patient performance on several secondary measures of cognitive function. Significant treatment effects were observed in the NYU Paragraph Delayed Recall test in the FE population. Significant improvements were observed in both the ITT and FE populations on the modified version of the ADAS-cog in the donepezil group. In addition, significant improvements favoring donepezil were observed in the FE population on the Digit Span Backwards and Symbol Digit Modalities tests. However, the results of secondary analyses should be interpreted with caution given the number of secondary measures employed. In addition, higher dropout rates in the donepezil group may have influenced outcomes in the FE population. Donepezil was safe and reasonably well tolerated in this study population.

Although the treatment effects on the primary end points were not significant, the results in secondary measures suggest directions for further study in this patient population. With no established methodology available, one aim of this study was to establish cognitive and functional measures sensitive to effects of donepezil treatment in patients with MCI. In selecting the primary and secondary outcome measures, the ADAS-cog was chosen as a secondary measure because it was believed to lack sensitivity to detect treatment differences in MCI subjects. However, the study results suggest that the modified ADAS-cog total score is sufficiently sensitive to be useful in studies of MCI patients. A number of reports have found that, relative to normal elderly, patients with MCI have measurable cognitive deficits that extend beyond the memory domain. For example, MCI patients have measurable deficits in language,[3,35,36] orientation,[7] and psychomotor/motor function.[36-38] Since test batteries such as the ADAS-cog tap into multiple domains of neuropsychologic functioning, it should not be surprising that this instrument may be particularly sensitive to a diffuse pattern of cognitive response likely to occur in treatment studies of patients with MCI. As such, consideration of its use as a primary efficacy variable in future studies of MCI appears warranted.

Several additional secondary efficacy measures were employed to evaluate other aspects of cognitive function thought to be impaired in MCI. Donepezil-related benefits in the Digit Span Backwards and Symbol Digit Modalities tests likely reflect improvement in attention, concentration, and psychomotor speed. It should be noted that subjects in both groups demonstrated some improvement on many cognitive tests, suggesting a preserved capacity to learn information, which, to our knowledge, has not been previously reported. Subjects also had a high level of education (mean 14.9 years) and practice effects may have influenced performance. It should be noted that the subjects in this study had predominantly amnestic MCI with a high level of education and a low level of depression, and lacked a medical history or current comorbidities that might account for their cognitive decline. It remains to be seen whether the performance and treatment response of this group is similar to a more heterogenous MCI cohort.

A higher proportion of patients in the donepezil group reported adverse events compared with the placebo group. Overall, the donepezil-placebo difference in the adverse event discontinuation rate was somewhat higher than in trials of similar design in

patients with AD. Although most adverse events were mild or moderate in severity, increased study withdrawals due to adverse events closely followed the forced dose escalation. As this study did not allow reduction in dose, all subjects unable to tolerate the 10 mg dose were dropped from the study. Perhaps patients earlier in the disease course have higher baseline levels of acetylcholine in the CNS than patients with mild to moderate AD and they may have increased awareness and lower tolerability of adverse events. Consideration should be given to allow more flexible dosing and to relaxing restrictions on dose adjustments to improve tolerability in future MCI trials.

The findings from this study have implications for the design of future efficacy trials for MCI as they provide important insights into outcome measures, sample and effect sizes, dosing, and study duration. In designing this study, investigators expected that there would be a decline in cognitive function of the placebo group over the 24-week observation period (as seen in patients with mild to moderate AD[13,14] and predicted if MCI is prodromal AD). The lack of decline in placebo-treated subjects over 6 months indicates that loss of cognitive function occurs more slowly in MCI subjects. Thus, efficacy trials of ChEIs may require trials of longer duration to adequately test for symptomatic treatment effects. Finally, the finding that patients with MCI show improvement on some cognitive tests may have implications for developing cognitive rehabilitation strategies for patients with MCI.

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Appendix

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ORIGINAL CONTRIBUTION

Memantine Treatment in Patients With Moderate to Severe Alzheimer Disease Already Receiving Donepezil

A Randomized Controlled Trial

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Context Memantine is a low- to moderate-affinity, uncompetitive *N*-methyl-D-aspartate receptor antagonist. Controlled trials have demonstrated the safety and efficacy of memantine monotherapy for patients with moderate to severe Alzheimer disease (AD) but no controlled trials of memantine in patients receiving a cholinesterase inhibitor have been performed.

Objective To compare the efficacy and safety of memantine vs placebo in patients with moderate to severe AD already receiving stable treatment with donepezil.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled clinical trial of 404 patients with moderate to severe AD and Mini-Mental State Examination scores of 5 to 14, who received stable doses of donepezil, conducted at 37 US sites between June 11, 2001, and June 3, 2002. A total of 322 patients (80%) completed the trial.

Interventions Participants were randomized to receive memantine (starting dose 5 mg/d, increased to 20 mg/d, n=203) or placebo (n=201) for 24 weeks.

Main Outcome Measures Change from baseline on the Severe Impairment Battery (SIB), a measure of cognition, and on a modified 19-item AD Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL$_{19}$). Secondary outcomes included a Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), the Neuropsychiatric Inventory, and the Behavioral Rating Scale for Geriatric Patients (BGP Care Dependency Subscale).

Results The change in total mean (SE) scores favored memantine vs placebo treatment for SIB (possible score range, 0-100), 0.9 (0.67) vs −2.5 (0.69), respectively ($P<.001$); ADCS-ADL$_{19}$ (possible score range, 0-54), −2.0 (0.50) vs −3.4 (0.51), respectively ($P=.03$); and the CIBIC-Plus (possible score range, 1-7), 4.41 (0.074) vs 4.66 (0.075), respectively ($P=.03$). All other secondary measures showed significant benefits of memantine treatment. Treatment discontinuations because of adverse events for memantine vs placebo were 15 (7.4%) vs 25 (12.4%), respectively.

Conclusions In patients with moderate to severe AD receiving stable doses of donepezil, memantine resulted in significantly better outcomes than placebo on measures of cognition, activities of daily living, global outcome, and behavior and was well tolerated. These results, together with previous studies, suggest that memantine represents a new approach for the treatment of patients with moderate to severe AD.

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ALZHEIMER DISEASE (AD) IS A neurodegenerative disorder characterized by cognitive decline, impaired performance of activities of daily living, and behavioral and psychiatric signs and symptoms. Pathological features of AD include intraneuronal neurofibrillary tangles containing abnormally phosphorylated tau protein, extracellular amyloid plaques containing the peptide β amyloid, neuronal cell death, and anatomic as well as functional impairment of neurotransmitter systems.[1,2] Alzheimer disease affects approximately 4.5 million people in the United States.[3] Treatments approved by the Food and Drug Administration were previously limited to monotherapy with cholinesterase inhibitors in patients with mild to moderate AD.[2] In October 2003, the Food and Drug Administration approved memantine for the treatment of moderate to severe AD; memantine is now available in more than 40 countries worldwide.

Memantine, a low- to moderate-affinity, uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, represents the first member of a new class of medications showing clinical benefit and good tolerability in AD. Although other NMDA receptor modulators (eg, milacemide and D-cycloserine) have failed in development as

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potential AD therapeutic agents,[4,5] memantine has exhibited efficacy and safety in a recent placebo-controlled trial in outpatients with moderate to severe AD and in an earlier study in nursing home patients with dementia.[6,7] An open-label study suggested that the combination of memantine and various cholinesterase inhibitors was well tolerated.[8] We hypothesized that administration of memantine to patients with moderate to severe AD receiving stable donepezil therapy would result in clinical benefit and would be safe and well tolerated.

METHODS

Participants

The trial was conducted from June 11, 2001, through June 3, 2002. Participants were recruited from 37 US sites; 404 patients who had a diagnosis of probable AD, according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association criteria, were enrolled. Inclusion criteria were as follows: Mini-Mental State Examination (MMSE) score of 5 to 14 at both screening and baseline; minimum age of 50 years; a recent magnetic resonance imaging or computed tomographic scan (within 12 months) consistent with a diagnosis of probable AD; ongoing cholinesterase inhibitor therapy with donepezil for more than 6 months before entrance into the trial and at a stable dose (5-10 mg/d) for at least 3 months; a knowledgeable and reliable caregiver to accompany the patient to research visits and oversee the administration of the investigational agent during the trial; residence in the community; ambulatory or ambulatory-aided (ie, walker or cane) ability; and stable medical condition. Patients were permitted to continue receiving stable doses of concomitant medications, including antidepressants, antihypertensives, anti-inflammatory drugs, atypical antipsychotics, antiparkinsonian drugs, anticoagulants, laxatives, diuretics, and sedatives/hypnotics.

Patients were excluded for clinically significant B_{12} or folate deficiency; active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease; other psychiatric or central nervous system disorders; computed tomographic or magnetic resonance imaging evidence of clinically significant central nervous system disorders other than probable AD; dementia complicated by other organic disease; or a modified Hachinski Ischemia Score[9] of more than 4 at screening. Written informed consent was obtained from the caregiver and either the patient (if possible) or a legally acceptable representative (if different from the caregiver) before the initiation of any study-specific procedures. The study was reviewed and approved by the institutional review board at each site.

Interventions

This study was a prospective randomized, placebo-controlled, parallel-group, fixed-dose trial in which participants were assigned to double-blind treatment for 24 weeks, with a 1- to 2-week single-blind placebo lead-in period before randomization solely to assess compliance. Patients were randomly allocated to 1 of the 2 treatment groups in permuted blocks of 4 in accordance with the randomization list generated and retained by the Department of Biostatistics at Forest Laboratories. At the baseline visit, each investigator sequentially assigned a randomization number to each patient. No individual patient randomization code was revealed during the trial.

Patients assigned to double-blind memantine treatment were titrated in 5-mg weekly increments from a starting dose of 5 mg/d to 20 mg/d (administered as two 5-mg tablets twice daily) at the beginning of week 4. Masked study medication was supplied to each study site for dispensation in blister packs at each visit. Drug and placebo tablets were visually identical and all patients received 4 tablets of study medication daily (in combinations of memantine [5 mg] and matching placebo tablets). All patients were to maintain stable donepezil therapy at entry dose as prescribed by the patient's physician for the duration of the study; adherence to this protocol was monitored by routine assessment of concomitant medication use. Any change in the dosing regimen or discontinuation of donepezil was recorded, and patients were discontinued from the study if the inclusion criterion of concomitant donepezil therapy was no longer met. From week 3 to the end of week 8 of double-blind treatment, transient dosage adjustments for memantine treatment were permitted for patients experiencing dose-limiting adverse events. All patients receiving memantine were required to receive the target dose of 20 mg/d by the end of week 8. Patients not tolerating the target dose by week 8 were disenrolled. Adherence with study medication was assessed by returned tablets and more than 95% of both treatment groups had more than 75% compliance (95% for the placebo-treatment group and 96.5% for the memantine-treatment group). Most patients who completed the double-blind phase entered the currently ongoing open-label extension.

Outcome Measures

Cognitive, functional, and global outcome measures were obtained at baseline and at the end of weeks 4, 8, 12, 18, and 24, unless otherwise specified. Patients who discontinued prematurely were evaluated during the final visit. The primary efficacy parameters were the change from baseline on the Severe Impairment Battery (SIB) and on a modified 19-item AD Cooperative Study–Activities of Daily Living Inventory ($ADCS\text{-}ADL_{19}$) at week 24.

The SIB is a 40-item test developed for the evaluation of cognitive dysfunction in patients with more severe AD. Six primary subscales assess memory, orientation, language, attention, visuospatial ability, and construction. In addition, the scale assesses praxis, social interaction, and orienting to name.[10,11] Validity, reliability, and sensitivity to longitudinal change have been established.[10,11] The SIB scores range from 0 to 100, with higher scores reflecting

higher levels of cognitive ability. The SIB was assessed at baseline and all subsequent visits.

The ADCS-ADL$_{19}$ was the second primary efficacy instrument.[12] This 19-item subset of the original 42-item inventory focuses on items appropriate for the assessment of later stages of dementia (ie, the level of independence in performing everyday tasks including eating, walking, grooming, telephone use, hobbies, complex tasks, and communications). The sensitivity and reliability of this modification have been established.[13] The ADCS-ADL$_{19}$ was administered as an interview to the patient's caregiver and focused on the performance of each activity of daily living during the previous 4 weeks. Possible scores range from 0 to 54. Higher scores reflect higher levels of functioning. The ADCS-ADL$_{19}$ was assessed at baseline and all subsequent visits.

The secondary outcomes included a Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus),[14] the Neuropsychiatric Inventory (NPI), and the Behavioral Rating Scale for Geriatric Patients (BGP). The CIBIC-Plus was administered according to the format of the Alzheimer Disease Cooperative Study–Clinician's Global Impression of Change. The CIBIC-Plus is used to assess the effect of medication on overall clinical status in patients with dementia, incorporating caregiver observations as well as patient interviews. Change is rated on a scale from 1 (marked improvement) to 7 (marked worsening). A global assessment of severity of illness was made at baseline; the CIBIC-Plus was assessed at all postbaseline visits.

The NPI was designed to assess the frequency and severity of behavioral symptoms in patients with dementia, based on an interview of the caregiver.[15] The 12-item version of the instrument was used with a total score ranging from 0 to 144. Higher scores reflect greater symptoms. The NPI was assessed at baseline, at the end of week 12, and at the final visit.

The BGP consists of 35 items (scored 0, 1, or 2 by the rater) assessing observable aspects of cognition, function, and behavior.[16] A higher score reflects worse function. The BGP care dependency subscale reflects cognitive and functional characteristics associated with increased need for care. The BGP was administered at baseline and the final visit.

The Functional Assessment Staging (FAST) was administered as an index of staging and not as a secondary outcome.[17] The FAST evaluates a patient's ability to perform daily and necessary life activities and is divided into 7 major stages, from normality (FAST stage 1) to severe dementia (FAST stage 7). Stages 6 and 7 are further divided into 11 substages (6a to 6e and 7a to 7f), each of which is based on specific functional deficits. The FAST was administered at baseline and the final visit.

Concomitant medications and vital signs were recorded at every visit; adverse events were recorded at baseline and all subsequent visits; and laboratory tests, electrocardiograms, and physical examinations were performed at the screening and final visits.

Sample Size

Assuming a hypothetical effect size of 0.35, a sample size of at least 170 patients in each treatment group provided a 90% power at a 2-sided α level of .05, based on a 2-sample t test for change from baseline to week 24 in both SIB and ADCS-ADL$_{19}$ scores.

Statistical Analyses

Three populations were considered in the statistical analyses. The randomized population consisted of all patients randomized into the study (n=404); the safety population consisted of all randomized patients who received at least 1 dose of double-blind study medication (n=403); the modified intent-to-treat population specified by the protocol consisted of patients in the safety population who completed at least 1 postbaseline SIB or ADCS-ADL$_{19}$ assessment (n=395). The statistical analysis plan for this study stipulated that only postbaseline data could be carried forward. Particularly for the CIBIC-Plus, it is not possible to carry forward baseline data because by definition this is a change score and is not applicable to baseline. All efficacy analyses were based on the modified intent-to-treat population. Primary efficacy analyses were conducted by using the last observation carried forward (LOCF) approach for missing data imputation. Supportive analyses were performed by using the observed case approach. Change from baseline was compared between memantine and placebo groups using a 2-way analysis of covariance, with treatment group and center as main effects and baseline total score as the covariate. The study was to be declared positive if memantine was statistically significantly better than placebo ($P<.05$) on both the SIB and ADCS-ADL$_{19}$. For categorical measures, the Cochran-Mantel-Haenszel statistic using modified Ridit scores (Van Elteren test) controlling for study center was used to compare distributions between memantine and placebo groups. No interim analyses were performed. SAS version 6.12 (SAS Institute, Cary, NC) was used for all analyses.

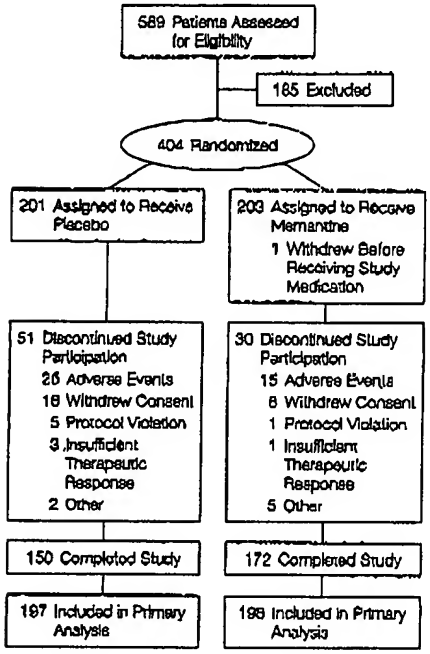
RESULTS

Participants

The trial profile is summarized in FIGURE 1. Of the 404 patients who entered the study, 201 were randomized to placebo and 203 were randomized to memantine (1 in the memantine group withdrew consent before receiving treatment). No patients were excluded during the placebo lead-in period for lack of compliance. Significantly more participants in the memantine group (n=172, 85.1%) completed the study than in the placebo group (n=150, 74.6%, $P=.01$). No patients discontinued because of changes in administration of donepezil.

The demographic and clinical characteristics of the 2 groups at baseline are summarized in TABLE 1. Patients in the memantine group were slightly heavier ($P=.003$) than those in the pla-

Figure 1. Study Flow



cebo group; retrospectively adding this variable to the analysis of covariance did not affect the primary outcomes. No clinically relevant group differences were observed for the duration of donepezil use before baseline or for any other characteristic at baseline. Most patients (87%) had a FAST rating between 4 and 6c. The most frequent medical conditions were not recorded, but the following body systems were noted to be affected at screening for placebo and memantine groups, respectively: eyes-ears-nose-throat (43% and 43%), neurological (34% and 38%), appearance/skin (40% and 33%), musculoskeletal (29% and 29%), cardiovascular (20% and 23%), abdomen (12% and 17%), head/neck (6% and 9%), other (10% and 9%), and pulmonary (3% and 5%). The most frequent medication classes (>20%) used during treatment with placebo and memantine, respectively, were vitamins (74% and 77%), analgesics (48% and 48%), antidepressants (36% and 36%), mineral supplements (22% and 27%), lipid-reducing agents (23% and 25%), anxiolytics/neuroleptics (26% and 22%), and anti-inflammatory agents (21% and 24%). There were no statistically significant differences between groups in the number or type of medical disorders experienced previously or at the time of enrollment, or in the number or type of concomitant medications used during the study.

Efficacy

Statistically significant benefits of treatment with memantine vs treatment with placebo were observed on all primary and secondary outcome measures as presented. TABLE 2 summarizes primary and secondary efficacy outcomes at week 24 and at end point, using both the observed case and LOCF analytical approaches.

Primary Outcomes

Analyses using the LOCF approach showed a statistically significant benefit of memantine treatment vs treatment with placebo on the SIB ($P<.001$) and the ADCS-ADL$_{19}$ ($P=.03$), as did analyses using the observed case approach ($P<.001$ for SIB; $P=.02$ for ADCS-ADL$_{19}$). Post hoc analyses including all randomized patients also showed statistically significant benefits consistent with analyses using the modified intent-to-treat population (for SIB, $P<.001$ and for ADCS-ADL$_{19}$, $P=.03$).

FIGURE 2 depicts the mean change from baseline by visit and at end point on the SIB by using observed case and LOCF, showing statistically significant differences between the memantine and placebo groups at all visits beginning at week 8; the mean SIB values for the patients receiving memantine remained above baseline throughout the trial. Figure 2 also depicts the mean change in total ADCS-ADL$_{19}$ from baseline by visit and at end point by using observed case and LOCF, respectively, showing a statistically significant difference ($P<.05$) from placebo beginning at week 4.

Secondary Outcomes

A CIBIC-Plus score was used as a measure of overall clinical response to therapy. The mean CIBIC-Plus score was statistically significantly better for the memantine group vs the placebo group using both observed case and LOCF (Table 2). Furthermore, 55% of the memantine group was rated as improved or unchanged vs 45% of the placebo group at end point. FIGURE 3 provides the distribution of CIBIC-Plus ratings at end point using LOCF analysis.

The total NPI score was significantly lower for the memantine group compared with the placebo group at week 24 ($P=.01$ with observed case analysis and $P=.002$ with LOCF), representing fewer behavioral disturbances and psychiatric symptoms for patients in the memantine group. The BGP care dependency subscale was also statistically significantly improved for the memantine group compared with the placebo group ($P=.001$ using observed case and $P=.001$ using LOCF; Table 2).

Safety and Tolerability

Overall treatment-emergent adverse events are summarized in TABLE 3. More participants (n=25, 12.4%) in the placebo-treated group discontinued prematurely because of adverse events than in the memantine group (n=15, 7.4%; Figure 1). The adverse event most often associated with discontinuation was confusion, resulting in discontinuation in 1.5% of patients in the placebo group and 2% in the memantine group.

Adverse events occurred in 72% of the placebo and 78% of the memantine groups. Most adverse events were rated as mild or moderate in severity and were judged to be not related to study drug for participants in both treatment groups. The only adverse events that occurred in at least 5% of the memantine group and with an incidence of at least twice that of the placebo group were confusion (7.9% vs 2.0%, respectively; $P=.01$) and headache (6.4% vs 2.5%, respectively; $P=.09$). By similar criteria, lower incidences of diarrhea (4.5% vs 8.5%) and fecal incontinence (2.0% vs 5.0%) were observed in the memantine group compared with the placebo group, respectively. Other gastrointes-

tinal effects of interest for patients receiving cholinesterase inhibitors included nausea, which was reported by 3.5% of the placebo group and 0.5% of the memantine group, and constipation, which was reported by 1.5% of the placebo group and 3.0% of the memantine group.

Of the patients who experienced confusion, 4 (25%) of 16 patients receiving memantine discontinued treatment because of this adverse event, whereas 3 (75%) of 4 patients receiving placebo did so. In most of the patients receiving memantine, confusion was rated as mild, occurred at a median of 32 days, and remitted within 2 weeks. In patients receiving placebo, confusion was more likely to be rated as severe, occurred at a median of 55 days, and did not remit. No patients discontinued because of headache, which usually lasted 1 day.

No clinically significant differences were detected between treatment groups in the mean change from baseline to end point or in the incidence of potentially clinically significant values for laboratory tests, vital sign measurements, or electrocardiogram parameters.

COMMENT

To our knowledge, this is the first published, prospective, double-blind, placebo-controlled study examining the benefits of an NMDA receptor antagonist in patients with AD receiving a stable dose of donepezil. Efficacy of memantine was significantly better than placebo for treatment of moderate to severe AD in community-dwelling patients. Specifically, measures of cognitive function, activities of daily living,

Table 1. Baseline Demographic and Clinical Characteristics*

Characteristics	Placebo (n = 201)	Memantine (n = 202)
Men	67 (33)	74 (37)
Women	134 (67)	128 (63)
Age, mean (SD), y	75.5 (8.73)	75.5 (8.45)
Weight, mean (SD), kg	66.4 (14.12)	70.7 (14.31)†
White race	186 (92.5)	182 (90.1)
MMSE score, mean (SD)	10.2 (2.98)	9.9 (3.13)
Duration of donepezil treatment, mean (SD), wk	129 (70.3)	126 (64.9)
Donepezil dose, mean (SD), mg	9.49 (1.88)	9.25 (1.79)
Any concurrent medical condition	149 (74.1)	149 (73.8)
Any concomitant medication during treatment	197 (98.0)	197 (97.5)
Tocopherol	120 (59.7)	131 (64.9)
Multivitamins	78 (38.8)	80 (39.6)
Acetylsalicylic acid	76 (37.8)	73 (36.1)
Ascorbic acid	35 (17.4)	43 (21.3)
Paracetamol	25 (12.4)	32 (15.8)
Ginkgo biloba	24 (11.9)	31 (15.3)
Calcium	21 (10.4)	26 (12.4)

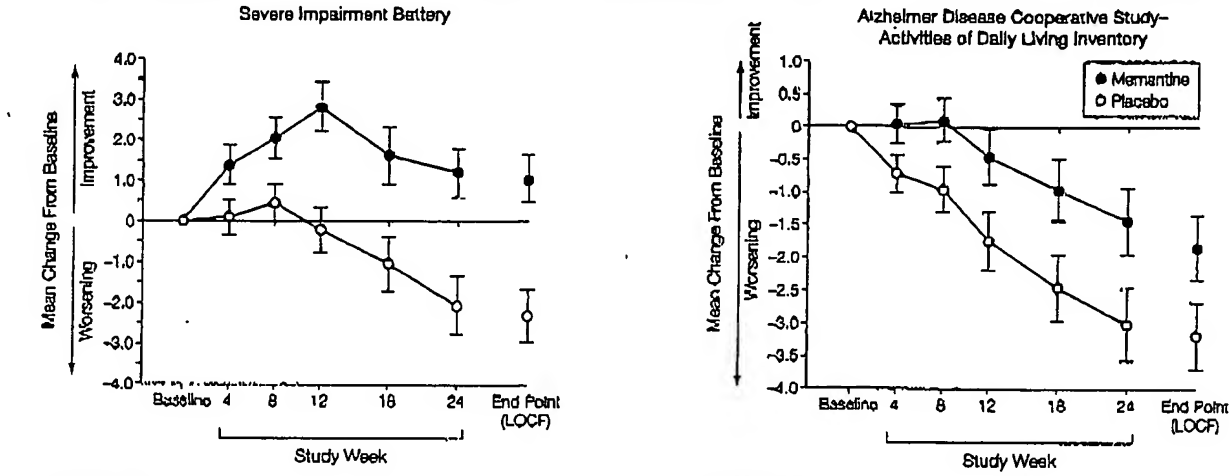
Abbreviation: MMSE, Mini-Mental State Examination.
*Data are No. (%) unless otherwise specified. One randomized patient discontinued the study prior to receiving any treatment and was not included in the analyses.
†$P = .003$.

Table 2. Efficacy Outcomes at Week 24 (Observed Case) and at End Point (LOCF)*

	Least Squares Mean Score (SE)							
			Change From Baseline					
	Baseline		End Point LOCF†			Week 24 Observed Case		
Outcome Measure	Placebo	Memantine	Placebo	Memantine	*P* Value	Placebo	Memantine	*P* Value
SIB	80.0 (1.13)	78.0 (1.11)	−2.5 (0.69)	0.9 (0.67)	<.001	−2.4 (0.74)	1.0 (0.70)	<.001
No. of patients	197	198	196	198		153	171	
ADCS-ADL$_{19}$	35.8 (0.74)	35.5 (0.73)	−3.4 (0.51)	−2.0 (0.50)	.03	−3.3 (0.55)	−1.7 (0.51)	.02
No. of patients	197	198	197	196		152	172	
CIBIC-Plus‡	NA	NA	4.66 (0.075)	4.41 (0.074)	.03	4.64 (0.087)	4.38 (0.081)	.03
No. of patients	197	198	196	198		152	172	
NPI	13.4 (1.08)	13.4 (1.07)	3.7 (0.99)	−0.1 (0.98)	.002	2.9 (1.06)	−0.5 (0.99)	.01
No. of patients	197	198	189	193		152	171	
BGP Care Dependency Subscale	9.6 (0.46)	9.5 (0.45)	2.3 (0.38)	0.6 (0.37)	.001	2.2 (0.40)	0.6 (0.37)	.001
No. of patients	196§	198	179	185		151	172	

Abbreviations: ADCS-ADL$_{19}$, 19-Item Alzheimer Disease Cooperative Study–Activities of Daily Living Inventory; BGP, Behavioral Rating Scale for Geriatric Patients; CIBIC-Plus, Clinician's Interview-Based Impression of Change Plus Caregiver Input; LOCF, last observation carried forward; NA, not applicable; NPI, Neuropsychiatric Inventory; SIB, Severe Impairment Battery.
*SIB range of possible scores, 0 to 100; higher score indicates better function. ADCS-ADL$_{19}$ range of possible scores, 0 to 54; higher score indicates better function. CIBIC-Plus was defined as a change score, therefore baseline values are not applicable; range of possible scores, 1 (marked improvement) to 7 (marked worsening). NPI range of possible scores, 0 to 144; higher scores indicate worse symptoms. BGP range of possible scores, 0 to 70; higher scores indicate worse function.
†For the end point LOCF approach, only postbaseline assessments were carried forward.
‡Arithmetic mean.
§One patient had an incomplete BGP baseline assessment and was not included.

Figure 2. SIB and ADCS-ADL$_{19}$ by Visit (Observed Case) and at End Point (LOCF)

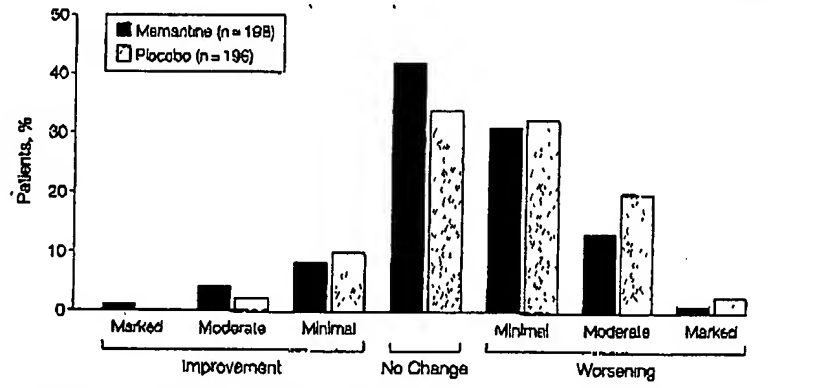


	Baseline	4	8	12	18	24	End Point (LOCF)
No. of Patients							
Memantine	198	197	190	185	181	171	198
Placebo	197	194	180	169	164	153	196
LS Mean Difference		-1.2	-1.5	-3.1	-2.7	-3.4	-3.4
P Value		.06	.03	<.001	.006	<.001	<.001

	Baseline	4	8	12	18	24	End Point (LOCF)
No. of Patients							
Memantine	198	198	190	185	181	172	198
Placebo	197	195	182	170	163	152	197
LS Mean Difference		-0.8	-1.1	-1.3	-1.4	-1.6	-1.4
P Value		.03	.01	.02	.03	.02	.03

SIB indicates Severe Impairment Battery; ADCS-ADL$_{19}$, 19-item Alzheimer Disease Cooperative Study–Activities of Daily Living Inventory; LOCF, last observation carried forward. For the Severe Impairment Battery, the mean (SD) score at baseline was 79.8 (14.18) for the placebo group and 77.8 (15.46) for the memantine group. For the Alzheimer Disease Cooperative Study–Activities of Daily Living Inventory, the mean (SD) score at baseline was 36.2 (9.32) for the placebo group and 35.9 (9.75) for the memantine group. Only patients with at least 1 postbaseline assessment were included in the LOCF analysis. The end point is the last nonmissing postbaseline assessment carried forward to end of study. Error bars indicate SEM.

Figure 3. Distribution of CIBIC-Plus Ratings at End Point (LOCF)



CIBIC-Plus indicates Clinician's Interview-Based Impression of Change Plus Caregiver Input; LOCF, last observation carried forward. P=.03 for the comparison between the distribution of values for the memantine and placebo groups, determined by the Cochran Mantel-Haenszel statistic using modified Ridit scores (Van Elteren test) controlling for study center.

behavior, and clinical global status were significantly improved with memantine compared with placebo. Treatment with memantine during the 6-month trial in patients with MMSE scores of 5 to 14 resulted in the maintenance of cognitive function (0.9 increase in SIB score compared with baseline), whereas treatment with placebo was associated with cognitive decline (2.5 decrease in SIB score compared with baseline). In comparison, the AD Cooperative Study group reported that for untreated patients with AD with MMSE scores of 5 to 9, the mean deterioration rate on the SIB was roughly 3.19 per month and for untreated patients with AD with MMSE scores of 10 to 15, the rate of change was 2.08 per month.[10] Treatment with memantine was associated with less decline on the CIBIC-Plus.

These efficacy findings confirm and extend results from previous placebo-controlled trials of memantine in dementia. A 12-week multicenter European trial[6] of memantine 10 mg/d was conducted in 166 nursing home residents with severe dementia, including both Alzheimer type and vascular dementias, diagnosed by *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria[18] (mean baseline MMSE of 6.3). Significant benefit of memantine vs placebo was observed on the Clinician's Global Impression of Change and the BGP care dependency subscale, and there were no clinically relevant differences in adverse events between memantine (21%) and placebo (22%) groups. A more recent 28-week multicenter US trial of memantine 20 mg/d monotherapy was conducted in 252 patients with moderate to severe probable AD by the National Institute of Neurological and Communicative Disorders and Stroke–

Alzheimer Disease and Related Disorders Association criteria and who were not permitted to receive a cholinesterase inhibitor.[7] Significant benefit of memantine treatment was observed on the ADCS-ADL$_{19}$, an assessment of function, and on the SIB, an assessment of cognition using both observed case and LOCF approaches, and on the CIBIC-Plus in the observed case but not the LOCF analysis. Adverse events were similar between the memantine (84%) and placebo (87%) groups.

Patients in the memantine monotherapy outpatient study[7] were more cognitively impaired (mean baseline MMSE of 7.9), more functionally impaired (mean baseline ADCS-ADL$_{19}$ score of approximately 27), and experienced more psychopathology (mean baseline NPI of approximately 20; rates of agitation as an adverse event in 32% and 18% of patients treated with placebo and memantine, respectively) than patients included in this trial. In addition, the magnitude of the memantine-placebo differences in outcomes common to both studies, as well as the magnitude of decline in most measures over time, was greater in the memantine monotherapy study than observed in this trial. This finding may be related to the higher severity of dementia in patients enrolled in the memantine monotherapy trial or because the present trial required donepezil therapy and permitted use of most psychotropics, factors which may have contributed to slower rates of decline in both the memantine and placebo groups. However, this type of inference is speculative given the absence of patients who were not treated with donepezil. Similar to the finding in the present trial, discontinuation rates because of adverse events in the monotherapy study were lower in patients receiving memantine than in those receiving placebo (10% vs 17%, respectively).[7] These trials support the efficacy of memantine for patients with moderate to severe AD.

Memantine administered at a dosage of 20 mg/d to patients receiving stable doses of donepezil was safe and well tolerated. Significantly more patients receiving placebo discontinued the trial than patients receiving memantine and the rate of discontinuation because of adverse events was lower in the memantine-treated group than in the placebo-treated group. The incidence of individual adverse events was generally similar in the 2 groups. Confusion, although occurring at a low frequency, was more common in patients receiving memantine than in those patients receiving placebo. However, it did not lead to a greater proportion of discontinuations and was mild in intensity and duration. The gastrointestinal adverse effects associated with cholinergic compounds were more commonly reported by patients receiving placebo, which was suggestive of a possible amelioration of these adverse events by the addition of memantine treatment to patients receiving a stable regimen of donepezil therapy. There were no clinically significant memantine-related mean changes in laboratory test results, vital signs, or electrocardiogram parameters.

There are limitations to the generalizability of our results. The trial did not address different doses or titration rates, the use of other cholinesterase inhibitors besides donepezil, or the impact of commencing memantine therapy before donepezil. Although there is no a priori reason to expect different results with other cholinesterase inhibitors, studies of memantine in combination with other cholinesterase inhibitors are being conducted to address this issue. Furthermore, results from an open-label European trial indicated that tolerability was not affected when donepezil or other cholinesterase inhibitors were administered to patients already receiving memantine or vice versa.[8] Preclinical studies show that memantine does not affect the inhibition of acetylcholinesterase by donepezil, nor does it bind to muscarinic receptors.[19-21] Furthermore, in healthy volunteers, no pharmacokinetic or pharmacodynamic interactions were observed between memantine and donepezil.[22] Although memantine has demonstrated positive cognitive effects in patients with mild to moderate vascular dementia, the efficacy of memantine administered alone or along with any cholinesterase inhibitor in other forms of dementia was not systematically evaluated in this trial.[23,24]

Table 3. Adverse Events Reported in at Least 5% of Patients in Either Treatment Group*

	Adverse Event, No. (%)	
	Placebo (n = 201)	Memantine (n = 202)
Agitation	24 (11.9)	19 (9.4)
Confusion	4 (2.0)	16 (7.9)
Fall	14 (7.0)	15 (7.4)
Influenza-like symptoms	13 (6.5)	15 (7.4)
Dizziness	16 (8.0)	14 (6.9)
Headache	5 (2.5)	13 (6.4)
Urinary tract infection	10 (5.0)	12 (5.9)
Urinary incontinence	6 (3.0)	11 (5.4)
Accidental injury	16 (8.0)	10 (5.0)
Upper respiratory tract infection	13 (6.5)	10 (5.0)
Peripheral edema	8 (4.0)	10 (5.0)
Diarrhea	17 (8.5)	9 (4.5)
Fecal incontinence	10 (5.0)	4 (2.0)

*Patients may have reported more than 1 adverse event.

The long-term effects of memantine and cholinesterase inhibitor treatment were not addressed in this double-blind trial but are the focus of the open-label extension and other ongoing trials. Considering that patients in this study had been receiving stable long-term donepezil therapy before enrollment, it is possible that participants were more likely to experience good tolerability and efficacy in the trial, perhaps because of having fewer medical problems or experiencing a slower rate of decline than patients without any prior AD treatment. However, the use of concomitant medications was typical for this elderly patient population and was similar between the groups. In addition, the dropout rate was approximately 15% in the memantine group vs approximately 25% in the placebo group, a phenomenon that perhaps led to an underestimation of the effect of memantine.

Drugs that target the glutamatergic system appear to have a therapeutic role in AD.[25,26] Memantine may block pathological activation of NMDA receptors while dissociating from the NMDA re-

ceptor channel during normal physiological conditions,[20] in theory improving cognition in states of glutamatergic excess. It is plausible that combining donepezil and memantine, which affect separate neurotransmitter systems, may confer independent clinical benefits. However, given the complex interconnection of different neurotransmitter systems, a synergistic mechanism is also plausible. Although the specific mechanisms and interactions between these therapies have not yet been defined, this and other studies demonstrate that memantine alone or together with a cholinesterase inhibitor results in significantly better outcomes than placebo in patients with moderate to severe AD.

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Author Contributions: Dr Tariot had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tariot, Gergel.

Acquisition of data: Tariot, Farlow, McDonald.

Analysis and interpretation of data: Tariot, Farlow, Grossberg, Graham, McDonald, Gergel.

Drafting of the manuscript: Tariot, Farlow, Grossberg, Graham.

Critical revision of the manuscript for important intellectual content: Tariot, Farlow, Grossberg, Graham, McDonald, Gergel.

Statistical expertise: Gergel.

Obtained funding: Gergel.

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Independent Analysis: Weichung J. Shih, PhD, from the University of Medicine and Dentistry of New Jersey provided an independent statistical analysis confirming the primary efficacy results.

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ORIGINAL ARTICLE

Memantine in Moderate-to-Severe Alzheimer's Disease

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ABSTRACT

BACKGROUND

Overstimulation of the N-methyl-D-aspartate (NMDA) receptor by glutamate is implicated in neurodegenerative disorders. Accordingly, we investigated memantine, an NMDA antagonist, for the treatment of Alzheimer's disease.

METHODS

Patients with moderate-to-severe Alzheimer's disease were randomly assigned to receive placebo or 20 mg of memantine daily for 28 weeks. The primary efficacy variables were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev). The secondary efficacy end points included the Severe Impairment Battery and other measures of cognition, function, and behavior. Treatment differences between base line and the end point were assessed. Missing observations were imputed by using the most recent previous observation (the last observation carried forward). The results were also analyzed with only the observed values included, without replacing the missing values (observed-cases analysis).

RESULTS

Two hundred fifty-two patients (67 percent women; mean age, 76 years) from 32 U.S. centers were enrolled. Of these, 181 (72 percent) completed the study and were evaluated at week 28. Seventy-one patients discontinued treatment prematurely (42 taking placebo and 29 taking memantine). Patients receiving memantine had a better outcome than those receiving placebo, according to the results of the CIBIC-Plus ($P=0.06$ with the last observation carried forward, $P=0.03$ for observed cases), the ADCS-ADLsev ($P=0.02$ with the last observation carried forward, $P=0.003$ for observed cases), and the Severe Impairment Battery ($P<0.001$ with the last observation carried forward, $P=0.002$ for observed cases). Memantine was not associated with a significant frequency of adverse events.

CONCLUSIONS

Antiglutamatergic treatment reduced clinical deterioration in moderate-to-severe Alzheimer's disease, a phase associated with distress for patients and burden on caregivers, for which other treatments are not available.

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ALZHEIMER'S DISEASE AFFECTS AT least 15 million persons throughout the world.[1,2] The number of persons with Alzheimer's disease is increasing substantially as populations age.[3] As Alzheimer's disease advances, patients become progressively impaired in both cognitive and functional capacities,[2,4] and the burden on caregivers increases. Pharmacologic treatments are currently approved for treating mild-to-moderate Alzheimer's disease.[5] However, there are no treatments for the more advanced stages of Alzheimer's disease.

Glutamate is the principal excitatory neurotransmitter in the brain.[6,7] Glutamatergic overstimulation may result in neuronal damage, a phenomenon that has been termed excitotoxicity. Such excitotoxicity ultimately leads to neuronal calcium overload and has been implicated in neurodegenerative disorders.[8] Glutamate stimulates a number of postsynaptic receptors, including the N-methyl-D-aspartate (NMDA) receptor, which has been particularly implicated in memory processes, dementia, and the pathogenesis of Alzheimer's disease.[9-11]

Memantine, an uncompetitive NMDA-receptor antagonist, could be of therapeutic value in Alzheimer's disease.[12] A recent study in patients with advanced dementia (Alzheimer's disease and vascular dementia) suggested therapeutic benefits.[13] Accordingly, we conducted a trial of the efficacy of memantine in outpatients with moderate-to-severe Alzheimer's disease.

METHODS

PATIENTS

Patients at least 50 years old who were residing in the community and had probable Alzheimer's disease according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV)[4] and of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[14] were recruited. The eligibility criteria included base-line Mini–Mental State Examination scores of 3 to 14,[15] a stage of 5 or 6 on the Global Deterioration Scale,[16] and a stage of 6a or greater on the Functional Assessment Staging instrument,[17] signifying the presence of dementia-related deficits in the ability to perform one or more basic activities of daily living. The patients had reliable caregivers and had undergone computed tomography (CT) or magnetic resonance imaging (MRI) of the brain within the previous 12 months.

Patients with vascular dementia, dementia or clinically significant neurologic disease due to conditions other than Alzheimer's disease, major depressive disorder, or a score greater than 4 on the modified Hachinski Ischemic Rating Scale[18] were excluded. Patients with clinically significant coexisting medical conditions or laboratory abnormalities were also excluded, as were patients receiving specific concomitant medications (anticonvulsant agents, antiparkinsonian agents, hypnotic agents, anxiolytic agents, neuroleptic agents, cholinomimetic agents, or any other investigational compounds). Patients who had been receiving stable antidepressant treatment for at least two months were eligible, and chloral hydrate could be used as a sedative or hypnotic, but not within 24 hours before an assessment.

STUDY DESIGN

In this 28-week, double-blind, parallel-group study, patients were randomly assigned to receive either memantine (20 mg per day; Merz) or an identical-appearing placebo. Randomization was stratified according to site with the use of RanCode (version 3.1) and in blocks of four, with staff at the individual sites blinded to the randomization process. The assigned treatment was discontinued if continuation represented a medical risk in the opinion of the study physician, or if the patient declined ongoing participation. Subjects who withdrew prematurely were asked to complete end-point measures at the time of early termination and to return at 28 weeks for a "retrieved-dropout visit," which included all end-point assessments. The results of an optional 24-week open-label study extension, in which all patients took memantine, are still being analyzed.

Thirty-two U.S. centers participated. The trial was conducted in compliance with the Declaration of Helsinki and its amendments and was approved by study-center institutional review boards. The eligible patients and responsible caregivers provided written informed consent.

Merz Pharmaceuticals provided study medication and funding and was involved in planning the design and protocol. Data analysis was performed by a contract research organization (Quintiles), along with the authors. The data are stored at Merz Pharmaceuticals.

EFFICACY VARIABLES

The prespecified primary efficacy variables were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) global

score (New York University version)[19] at 28 weeks and the change from base line to week 28 in the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL)[20] modified for more severe dementia (ADCS-ADLsev).[21] If values from the 28-week observation were not available, the last observed value was used. Assessments were conducted at base line, at mid-study (week 12), and at the end of treatment (week 28) or at early termination, with a 28-week retrieved-dropout visit when possible.

The CIBIC-Plus measures overall global change relative to base line and is scored on a seven-point scale ranging from 1 (markedly improved) to 7 (markedly worse). The domains of cognition (assessed by patient interview), function (caregiver interview), and behavior (separate patient and caregiver interviews) are systematically evaluated. Experienced clinicians, blinded to adverse events and other study assessments, conducted separate interviews with study patients and caregivers to assess overall change on the CIBIC-Plus. To ensure consistency, the same clinician completed all CIBIC-Plus interviews for each study patient and associated caregiver wherever possible.

The ADCS-ADL is a structured questionnaire originally created to assess functional capacity over a broad range of severity of dementia. Each item consists of a series of hierarchical questions designed to determine a patient's ability to perform one of the activities of daily living, ranging from total independence to total inability. A subgroup of 19 individually validated items (the ADCS-ADLsev) was used; a total score of 54 signified optimal performance, and lower scores indicated worse performance. Caregivers assessed a patient's activities during the preceding four-week interval. The differences in total scores were analyzed.

In addition, six other efficacy variables were measured. The Severe Impairment Battery[22,23] was designed to evaluate cognitive performance in advanced Alzheimer's disease. A 51-item scale, it assesses social interaction, memory, language, visuospatial ability, attention, praxis, and construction. The scores range from 0 (greatest impairment) to 100. The Severe Impairment Battery was part of a predefined responder analysis. The Mini–Mental State Examination[15] is a 30-point scale that measures cognitive function, with higher scores indicating better function. The Global Deterioration Scale[16] is a seven-stage scale that assesses overall cognitive and functional capacity on the basis of observations of the patient and reports from the caregiver. Higher stages signify greater impairment.

The Functional Assessment Staging scale[17] assesses the magnitude of progressive functional deterioration in patients with dementia by identifying characteristic progressive disabilities. Its seven major stages range from normal (stage 1) to severe dementia (stage 7). Five substages in stage 6, corresponding to the loss of ability to independently dress, bathe, and handle proper mechanics and cleanliness in using the toilet, and to remain continent, respectively, of urine and feces and six substages in stage 7, corresponding to the loss of speech, ambulation, and other motor capacities, are assessed. The Neuropsychiatric Inventory[24] assesses neuropsychiatric disturbances with a 12-item scale based on information from the caregiver regarding the patient's behavior and associated distress felt by the caregiver. The scores range from 0 to 144 for the patient-assessment rating and from 0 to 60 for the caregiver-distress rating, with 0 indicating the optimum in each case. The Resource Utilization in Dementia[25] instrument was designed to assess the burden on the caregiver and to provide Alzheimer's disease–related health economics data through structured interviews with caregivers. To assess the clinical relevance of treatment effects further, a multifactor responder analysis was predefined.

Measures of safety, assessed at specified intervals, included neurologic and physical examinations, measurement of vital signs, electrocardiography, laboratory tests (hematologic tests, blood chemical values, and urinalysis), and recording of adverse events.

STATISTICAL ANALYSIS

The main efficacy analysis was based on the randomized patients who received at least one assessment after base line. This analysis included both those who completed the study and those who discontinued their assigned treatment prematurely. For the latter, the efficacy observation at week 28 was imputed from the last available observation carried forward.[26] Three additional analyses were also performed to adjust for missing values. One analysis was identical to the primary analysis, except that the actual retrieved-dropout values at week 28 were used when available. A second analysis included patients for whom no value after base line was available in addition to the intention-to-treat population and assumed no change in the outcome

measures for these patients. In the third analysis, missing values were replaced for those with no value after base line by the mean observed value for decline in the placebo group. An observed-cases analysis was also performed based on data for all randomized patients who were available for evaluation at week 28.

Efficacy outcomes were analyzed by application of the Wilcoxon–Mann–Whitney test for independent samples to the change from base line. There were no interim analyses. The prespecified group with an individual response was defined as the patients who improved or had no deterioration on the CIBIC-Plus and who improved or had no deterioration on either the ADCS-ADLsev or the Severe Impairment Battery. All patients were included in the safety analysis. All reported P values are two-sided.

RESULTS

STUDY POPULATION

Of 345 patients screened between August 1998 and April 1999 at 32 U.S. centers, 252 were randomly assigned to study groups. Seventy-one of the patients (42 of the 126 assigned to placebo and 29 of the 126 assigned to memantine) discontinued their assigned treatment before week 28, and the remaining 181 completed the double-blind portion of the study. Five patients were excluded from the analysis of the ADCS-ADLsev results and 16 from the analysis of the CIBIC-Plus results because they had not been assessed after the base-line assessment. The mean (±SD) duration of treatment for both groups was 24±8 weeks. Only 5 of the 71 patients who left the study returned for a retrieved-dropout visit at week 28. Premature discontinuations were due to adverse events in 22 of the patients in the placebo group (17 percent) and 13 of the patients in the memantine group (10 percent). Other major reasons for discontinuation included the patient's refusal of ongoing participation (14 patients receiving placebo [11 percent] and 12 patients receiving memantine [10 percent]), death (4 patients receiving placebo [3 percent] and 1 patient receiving memantine [1 percent]), protocol violation (3 patients receiving placebo [2 percent] and 3 patients receiving memantine [2 percent]), and change of caregiver (2 patients receiving placebo [2 percent] and none receiving memantine). Patients could have multiple reasons for discontinuation.

Table 1. Base-Line Characteristics of the Intention-to-Treat Population.*

Characteristic	Memantine (N=126)		Placebo (N=126)		Total (N=252)
	Completed Study (N=97)	Did Not Complete Study (N=29)	Completed Study (N=84)	Did Not Complete Study (N=42)	
Sex — no. (%)					
Female	70 (72.2)	21 (72.4)	55 (65.5)	24 (57.1)	170 (67.5)
Male	27 (27.8)	8 (27.6)	29 (34.5)	18 (42.9)	82 (32.5)
Age — yr	75.5±8.16	77.3±9.17	75.8±7.28	77.5±8.61	76.1±8.07
Education — yr	12.3±3.06	13.0±3.14	12.9±3.14	11.7±2.91	12.5±3.09
Race — no. (%)					
White	85 (87.6)	27 (93.1)	75 (89.3)	40 (95.2)	227 (90.1)
Black	4 (4.1)	1 (3.4)	4 (4.8)	2 (4.8)	11 (4.4)
Other	8 (8.2)	1 (3.4)	5 (6.0)	0	14 (5.6)
MMSE score	7.8±3.76	7.6±3.67	8.1±3.60	7.9±3.54	7.9±3.64
GDS stage — no. (%)					
5	46 (47.4)	13 (44.8)	41 (48.8)	12 (28.6)	112 (44.4)
6	51 (52.6)	16 (55.2)	43 (51.2)	30 (71.4)	140 (55.6)

* The intention-to-treat population included all randomized patients. Plus–minus values are means ±SD. MMSE denotes Mini–Mental State Examination, and GDS Global Deterioration Scale.

The base-line characteristics were similar in the two treatment groups (Table 1). Of the randomized patients, 67 percent were female, and the mean age was 76 years. The mean base-line score on the Mini–Mental State Examination for the study population was 7.9.

EFFICACY

The base-line scores and the results based on analyses with the last observation carried forward and analyses of observed cases for the efficacy variables are shown in Table 2. The CIBIC-Plus ratings at the end point (mean difference between the groups, 0.3; P=0.06) and week 28 (mean difference, 0.3; P=0.03) supported the effectiveness of memantine (Fig. 1A).

The total ADCS-ADLsev scores at base line were similar in the two groups (27.4 in the placebo group and 26.8 in the memantine group) (Table 2). At the end point and at week 28 (Fig. 1B), there was significantly less deterioration in the memantine group than in the placebo group (in the analysis with the last observation carried forward, the mean difference was 2.1 [P=0.02]; in the observed-cases analysis, the mean difference was 3.4 [P=0.003]).

The Severe Impairment Battery showed significant differences favoring memantine (P<0.001 with the last observation carried forward, P=0.002 for observed cases) (Fig. 2A). On the basis of the predetermined definition of a response in the study protocol, 29 percent of the patients receiving memantine and 10 percent of those receiving placebo had a response (P<0.001).

Memantine-treated patients showed significantly less deterioration in their functional Alzheimer's disease stage, as measured by the Functional Assessment Staging score (P=0.02 with the last observation carried forward, P=0.007 for observed cases) (Fig. 2B). In the analysis of the intention-to-treat population with the last observation carried forward and at week 28 no significant differences were observed between treatment groups in the Mini–Mental State Examination score, Global Deterioration Scale stage, or Neuropsychiatric Inventory score.

Additional analyses were performed with different strategies used for missing values, as described above. The results were unchanged in each of these analyses.

A subgroup analysis examined whether efficacy was seen in both patients with moderate Alzheimer's

Table 2. Results of the Efficacy Analysis.*

Measure	Base Line		Analysis with Last Observation Carried Forward (Change from Base Line at End Point)			Analysis of Observed Cases (Change from Base Line at Week 28)		
	Memantine	Placebo	Memantine	Placebo	P Value†	Memantine	Placebo	P Value†
CIBIC-Plus‡								
Score	NA	NA	4.5±1.12	4.8±1.09	0.06	4.4±1.12	4.7±1.13	0.03
No. of patients	126	126	118	118		97	84	
ADCS-ADLsev§								
Score	26.8	27.4	−3.1±6.79	−5.2±6.33	0.02	−2.5±6.27	−5.9±6.78	0.003
No. of patients	126	126	124	123		97	84	
SIB								
Score	65.9	68.3	−4.0±11.34	−10.1±13.50	<0.001	−4.5±11.48	−10.2±12.66	0.002
No. of patients	126	126	124	123		96	83	
MMSE								
Score	7.7	8.1	−0.5±2.40	−1.2±3.02	0.18	−0.6±2.61	−0.9±3.09	0.68
No. of patients	126	126	124	124		97	82	
FAST¶								
Score	2.8	2.8	0.2±1.24	0.6±1.39	0.02	0.1±1.24	0.5±1.38	0.007
No. of patients	126	126	121	118		97	84	
GDS								
Score	5.5	5.6	0.1±0.47	0.2±0.48	0.11	0.1±0.49	0.2±0.48	0.16
No. of patients	126	126	121	119		97	84	
NPI‖								
Score	21.4	19.5	0.5±15.76	3.8±16.06	0.33	0.1±15.92	2.9±16.13	0.60
No. of patients	126	126	120	119		97	84	

* CI denotes confidence interval, CIBIC-Plus Clinician's Interview-Based Impression of Change Plus Caregiver Input, NA not applicable, ADCS-ADLsev Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (modified for severe dementia), SIB Severe Impairment Battery, MMSE Mini–Mental State Examination, FAST Functional Assessment Staging, GDS Global Deterioration Scale, and NPI Neuropsychiatric Inventory. The analysis with the last observation carried forward was performed with the intention-to-treat population. For this analysis, the numbers of patients fulfilling the intention-to-treat criteria are given in parentheses. The observed-cases analysis was performed with 181 patients observed at week 28. Plus–minus values are means ±SD.

† P values are based on the Wilcoxon–Mann–Whitney test for between-treatment comparisons.

‡ The CIBIC-Plus is a change score. By design the base-line score, "no change," is set at 4.00. Higher values at subsequent measurements indicate worsening. The end-point and week 28 values are actual mean ratings. The 95 percent confidence intervals for the differences between groups were −0.51 to 0.02 for the change from base line at the end point and −0.69 to −0.03 for the change from base line at week 28.

§ The 95 percent confidence intervals for the differences between groups were 0.49 to 3.78 for the change from base line at the end point and 1.45 to 5.28 for the change from base line at week 28.

¶ The FAST scores were calculated by enumerating the FAST stages and substages as follows: stage 3 (a score of −2) through 5 (0) and substage 6a (1) through substage 7f (11).[17]

‖ The NPI scores are from the patient assessments.

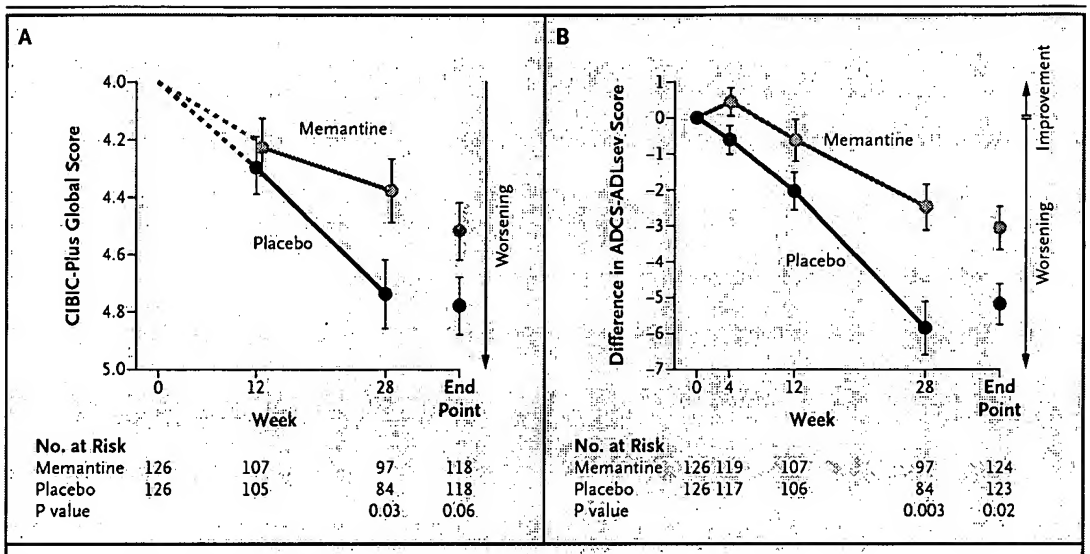

Figure 1. Primary Efficacy Variables.

The mean (±SE) scores at each specified time in the observed-cases analysis are shown. The boxes indicate the mean (±SE) at the end point in the analysis with the last observation carried forward in the intention-to-treat population. Panel A shows the change from base line in the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) global scores. Panel B shows the change from base line in the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory, modified for severe dementia (ADCS-ADLsev).

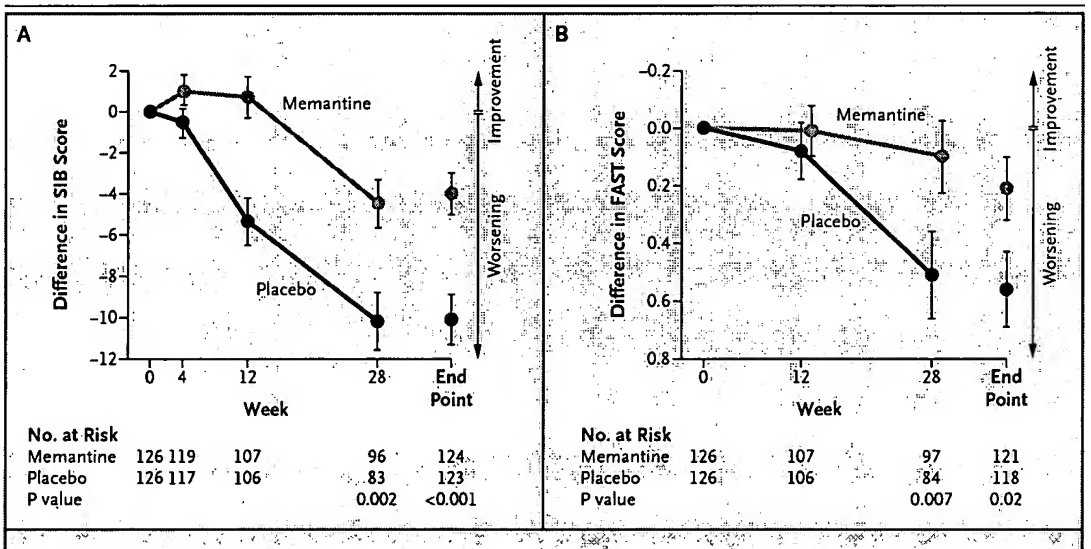

Figure 2. Other Efficacy Variables.

The mean (±SE) scores at each specified time in the observed-cases analysis are shown. The boxes indicate the mean (±SE) at the end point in the analysis with the last observation carried forward in the intention-to-treat population. Panel A shows the change from base line in Severe Impairment Battery (SIB) scores. Panel B shows the change from base line in Functional Assessment Staging (FAST) scores, calculated by enumerating the stages and substages as follows: stage 3 (−2) through stage 5 (0) and substage 6a (1) through substage 7f (11).

disease (Mini–Mental State Examination score, 10 to 14) and those with severe Alzheimer's disease (Mini–Mental State Examination score, less than 10). A benefit of memantine as compared with placebo was suggested for all outcome measures in both groups.

The required caregiver time, as assessed by the Resource Utilization in Dementia score, was analyzed in the intention-to-treat population with the last observation carried forward. The result was statistically significant, indicating that caregivers spent less time with patients receiving memantine (difference between treatment groups, 45.8 hours per month; 95 percent confidence interval, 10.37 to 81.27; P=0.01).

Table 3. Most Frequently Reported Adverse Events.*

Adverse Event	Memantine (N=126)	Placebo (N=126)
	no. of patients (%)	
Any adverse event	106 (84)	109 (87)
Agitation	23 (18)	40 (32)
Urinary incontinence	14 (11)	14 (11)
Urinary tract infection	7 (6)	17 (13)
Insomnia	13 (10)	10 (8)
Diarrhea	12 (10)	10 (8)

* Adverse events occurring in at least 10 percent of the patients in either treatment group are reported.

SAFETY AND TOLERABILITY

As expected in this population with moderate-to-severe illness, the majority of patients had adverse events during the study (84 percent with memantine and 87 percent with placebo). However, most adverse events were mild to moderate in severity and were either not related or unlikely to be related to the study medication (Table 3). The incidence rates for the frequently reported adverse events in the memantine group were no more than 2 percent higher than in the placebo group. There were no clinically relevant differences between patients in the memantine and placebo groups in base-line assessments of clinical laboratory values, electrocardiographic results, or measurements of vital signs.

More patients receiving placebo than patients receiving memantine discontinued the study prematurely because of adverse events (22 [17 percent] vs. 13 [10 percent]). Agitation was the most common reason for discontinuation (7 percent of those receiving placebo and 5 percent of those receiving memantine). Serious adverse events were reported in 23 patients receiving placebo (18 percent) and 16 patients receiving memantine (13 percent). There were seven deaths, two of which occurred in the memantine group. Two of these patients died within the 30-day period after the last dose of study medication. Most of the serious adverse events, including all of the deaths, were considered to be unrelated to the study medication.

DISCUSSION

This study provides evidence that modulation of NMDA receptors to reduce glutamate-induced excitotoxicity alleviates the symptoms of Alzheimer's disease. This novel neurochemical approach is distinct from the cholinomimetic mechanism of all currently approved treatments for Alzheimer's disease.

This trial studied patients whose moderate-to-severe Alzheimer's disease compromised their ability to perform both instrumental and basic activities of daily living independently.[17] More than 95 percent of patients were in Functional Assessment Staging stage 6. All patients had difficulty putting on clothing independently, and many also had difficulties with handling the mechanics of bathing and toilet use, and some patients also had difficulties maintaining continence. The significant differences observed in favor of the memantine group on the ADCS-ADLsev, the Functional Assessment Staging ratings, and the Severe Impairment Battery suggest reduced decline in these critical capacities, which was apparent in the global assessment of the patients (CIBIC-Plus in the observed-cases analysis).

The clinical relevance of treatment effects has been an issue in all trials of medication for Alzheimer's disease. Point differences between drug- and placebo-treated patients on quantitative scales do not necessarily indicate that these effects are clinically meaningful. Response analyses (rates of individual response) are often performed to illustrate the clinical relevance of results. In the present study, a significant difference in the predefined criterion for a response, which incorporated multiple end points, was observed. The treatment effects seen in the areas of cognition and function seemed to translate into improvements in the patients' behavior (less agitation in the adverse-events reports) and

mitigation of the burden on caregivers (fewer hours spent assisting the patient).

The results of the present study cannot be directly compared with those of studies of other antidementia drugs (tacrine, donepezil, rivastigmine, and galantamine); virtually all published studies with these compounds have been performed in patients with mild-to-moderate Alzheimer's disease. An exception is a recent study of donepezil by Feldman et al.[27] However, even that study included patients with less severe disease (the mean Mini–Mental State Examination score at base line was 12) than those in the present trial, whose mean Mini–Mental State Examination score at base line was less than 8. The treatment effects of memantine in the present study and donepezil in the study by Feldman et al. are of similar size for the common end points, the CIBIC-Plus and the Severe Impairment Battery. Cholinergic compounds have gastrointestinal side effects, whereas the tolerability of memantine in this study was found to be excellent. Future studies will need to examine whether memantine treatment and cholinergic treatment may ultimately prove to be complementary or even synergistic.

There are notable limitations to this study. The dropout rate for the total study population was 28 percent, which is probably attributable to the relatively severe stage of disease in the study patients. The withdrawal rate was higher in the placebo group (33 percent) than in the memantine group (23 percent). The failure to obtain information at week 28 for the majority of patients who discontinued the study prematurely limits the interpretation of the results. However, the average duration of randomly assigned therapy for patients in this 28-week trial was 24 weeks for both study groups. In three analyses, the effects of different strategies for replacing missing observations for all patients assigned to treatment were investigated, and the results did not change materially. Thus, our data indicate that memantine reduces decline in patients with moderate-to-severe Alzheimer's disease.

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APPENDIX

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